Systematic reviews of diagnostic test accuracy

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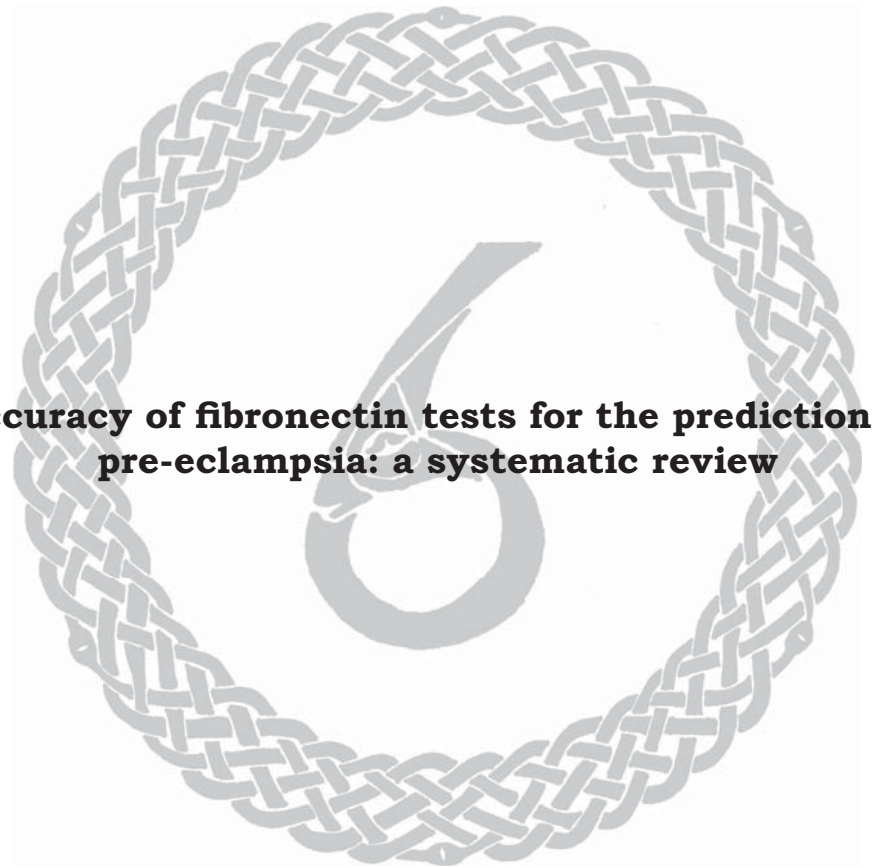

Accuracy of fibronectin tests for the prediction of pre-eclampsia: a systematic review

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Abstract

Background: The purpose of this study was to review systematically all studies that assessed the accuracy of maternal plasma fibronectin as a serum marker for early prediction of pre-eclampsia.

Methods: We therefore assessed studies that reported on fibronectin as serum marker for pre-eclampsia before the 25th gestational week. For the selected studies, sensitivity and specificity were calculated and plotted in ROC-space.

Results: We included twelve studies, of which only five studies reported sufficient data to calculate accuracy estimates, such as sensitivity and specificity. These five studies reported on 573 pregnant women of whom 109 developed pre-eclampsia. At a sensitivity of at least 50%, specificities ranged between 72 and 96% for cellular fibronectin. For total fibronectin, these numbers were 42 to 94%.

Conclusions: Fibronectin seems to be a promising marker for the prediction of pre-eclampsia. However, further studies are needed to determine whether the accuracy of this test is sufficient to be clinically relevant.

6.1 Background

Pre-eclampsia is among the largest single causes of maternal and foetal mortality and morbidity world wide[1-3]. It has a long pre-clinical phase before signs become clinically manifest during the second half of pregnancy. Good prediction will enable to redirect intensified prenatal care from all pregnant women to those women and foetuses who are at higher risk, and to more effectively evaluate interventions for prevention of pre-eclampsia[4-8]. Also, women at high risk could benefit from increased surveillance, preventive therapies like aspirin and early diagnosis[9,10].

Maternal and perinatal mortality and morbidity result from maternal organ failure, foetal growth restriction and premature delivery. Maternal endothelial damage and inadequate placental development are both involved in the genesis of pre-eclampsia[11]. Therefore, a number of products released from the placenta and biochemical markers for endothelial damage were tested for their ability to predict the onset of pre-eclampsia. One of these possible markers was fibronectin (Fn), a glycoprotein that plays a role in a variety of biological functions.

Several subtypes of Fn exist. Inflammation, vascular injury and malignancy are generally associated with increased expression of the ED-A (also called ED-1+ or oncofoetal Fn) and ED-B (also called ED-2+) forms of Fn, particularly in the blood vessel walls[12-14]. ED-A (oncofoetal) Fn is also released by the placenta and has been used as a predictor for preterm birth[15,16].

Several studies showed that, on average, women destined to develop pre-eclampsia had higher plasma Fn concentrations than (pregnant) controls. However, these studies differ in, for example the type of test that is evaluated, the study population, and scientific rigour. Earlier reviews about the prediction of pre-eclampsia that also included Fn measurements reported conflicting results or did not differentiate between ED-A or ED-B Fn (only 5% of all Fn in plasma) and total Fn (all subtypes of Fn)[17-26]. The most recent review reported low predictive accuracy of the Fn tests[18]. However, this was based on only one study. In addition, this review has been criticized for performing the crucial steps of screening of bibliographies and data-extraction using a single reviewer only and suboptimal statistical methods[27].

We conducted a systematic review of the available evidence to obtain valid and reliable estimates of predictive accuracy of Fn assays for the early (< 25th gestational week) prediction of pre-eclampsia.

6.2 Methods

6.2.1 Study selection and data extraction procedures

We developed an electronic search strategy for the general databases: MEDLINE (1953-2004), and EMBASE (1980-2004), and specialist databases: The Cochrane Library (2004:3), and MEDION (1974-2004; www.mediondatabase.nl). This search was updated in April, 2006. The search strategy consisted of MeSH and keyword terms related to pre-eclampsia combined with methodological filters for identification of diagnostic test and aetiological studies[28,29]. Reference lists of review articles and eligible primary studies were checked to identify cited articles not captured by electronic searches. The electronic search strategy is available from the authors.

Studies were selected in a three-stage process. First, titles and/or abstracts of all references (Reference Manager 10.0) were scrutinized by one reviewer for studies that reported on any test used in predicting pre-eclampsia (JC, GtR, JvdP and BWM). Then, for this particular review, a second reviewer scrutinized all references with "fibronectin" as keyword or as word in title or abstract to ensure independent duplicate selection (JC). Final in-/ exclusion decisions were made after independent duplicate examination of the full manuscripts of selected references (JvdP and ML). Studies were included if they reported on Fn testing in maternal serum or plasma before the 25th gestational week (mean). Language restrictions were not applied. Any disagreements were resolved by consensus and, if necessary, by a third reviewer (JC). For each included article, data on study characteristics (both clinical and methodological) and on test accuracy were extracted independently by two reviewers (JvdP and ML) on piloted data extraction forms. Disagreements were resolved by consensus. Study characteristics consisted of women's risk classifications, characteristics of the index test and the reference standard.

6.2.2 Quality assessment

The methodological quality of the selected primary studies was assessed using predefined criteria based on elements of study design, conduct and analysis which are likely to have a direct relationship to bias in a test accuracy study[30-32]. For this purpose, we used the QUADAS list[33], a tool for quality assessment of diagnostic accuracy studies. This checklist was adapted with respect to timing of the test, patient spectrum (some patient characteristics, such as being normotensive and non-proteinuric, are part of the reference standard), partial verification and the index test being part of the reference standard. We also assessed the occurrence of a potential treatment paradox (mainly the use of antihypertensive drugs; yes or no), because this review deals with prediction instead of diagnosis. Patient spectrum was judged representative for general pregnant populations when eligible women were consecutively recruited and the incidence of pre-eclampsia did not exceed 4%.

6.2.3 Data synthesis: main analysis

For each study, we constructed a 2-by-2 table cross-classifying Fn results and the occurrence of pre-eclampsia. Sensitivity, specificity and likelihood ratios were calculated. We assessed the heterogeneity of results between studies looking at the distribution of sensitivities and specificities in the receiver operating characteristic (ROC) plot. Because of the differences in study characteristics, we considered meta-analysis to generate summary estimates not appropriate.

6.3 Results

6.3.1 Included studies

Figure 6.1 summarizes the selection process for studies on Fn and prediction of pre-eclampsia. Twelve studies[34-45] met the inclusion criteria, eight cohort studies[34-41] and four nested case control studies[42-45] (Table 6.1). All case control studies selected incident cases of pre-eclampsia and non pre-eclamptic controls. Three were matched case control studies[42,44,45], matching occurred on factors such as maternal and gestational age. No studies classified the cases into severe and mild pre-eclampsia. The cohort studies were all conducted in hospitals providing secondary or tertiary

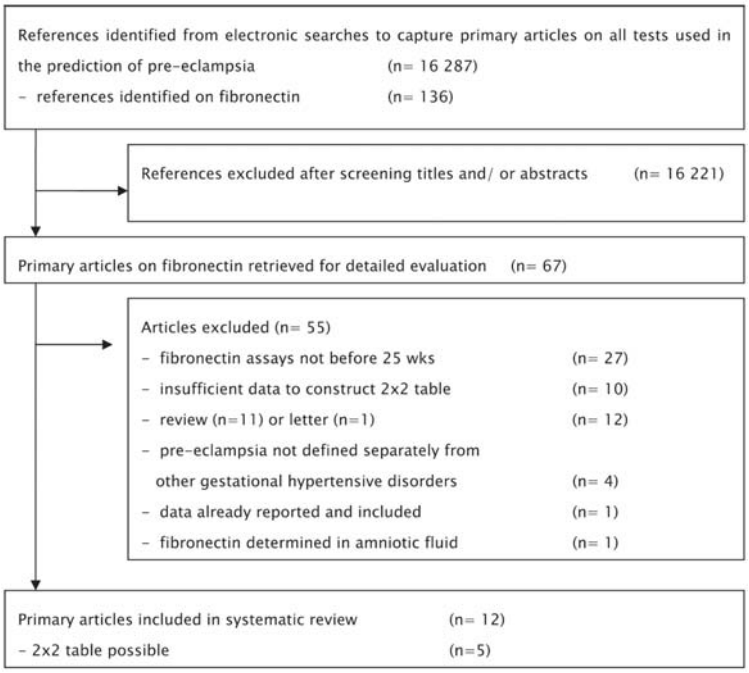

Figure 6.1. Study selection process for this review.
Of the finally included 12 primary studies, five reported sufficient data for 2x2 tables.

Table 6.1. Key characteristics of included studies.

First Author (Year)	Setting (no. centres)	Country	Design	n **	Incidence of PE (%)	Inclusion Criteria	Exclusion Criteria	Reference Standard	Fn fraction measured
Lockwood [44] (1990)	Primary care (1)	USA	nested and matched CC	57	4.50	Singleton pregnancies, normotensive <20 wks gest; not all were primigravid.	IDDM, CH, abruptio placentae and infections, history of previous PE	BP 140/90 mmHg, rise in systolic or diastolic BP of 30 resp. 15 mmHg (in seated position, Korotkoff phase V) ; 1 gm/L proteinuria; at least two occasions >6 h apart.	total Fn and ED-A Fn
Taylor[45] (1991)	Mixed settings (2)	USA	nested and matched CC	38	NR	Normotensive and non-proteinuric <20 wks gest.	Identification of any chronic metabolic disease, evidence of illicit drug use or the failure of elevated BP, hyperuricemia or proteinuria to resolve within 12 weeks after delivery.	Rise in systolic or diastolic BP of 30 resp. 15 mmHg (in seated position, Korotkoff phase V); proteinuria ≥0.5 gm/24 h or ≥30 mg/dl in a catheterized specimen; hyperuricemia.	ED-B Fn
Friedman[43] (1992)	Secondary / tertiary care (1)	USA*	nested CC	20	NR	NR	NR	BP 140/90 mmHg, rise in systolic or diastolic BP of 30 resp. 15 mmHg; proteinuria (≥1+ catheterized or ≥2+ voided); and hyperuricemia.	Fetal Fn
Halligan[34] (1994)	Mixed settings (NR)	Ireland*	cohort	36	11.1	Primigravid.	NR	Referred to Davey and McGillivray, 1988.	Total plasma Fn
Jones[36] (1996)	Secondary / tertiary care (1)	Australia	cohort	171	19.3	Singleton pregnancies, normotensive <20 wks gest.	NR	Referred to Beischer & Mackay	Serum Fn
Soltan[39] (1996)	Secondary / tertiary care (1)	Egypt	cohort	88	NR	Normotensive and non-proteinuric <20 wks gest.	IDDM, CRD, history of cardiovascular or renal disease, aspirin therapy, antiprostaglandins, calcium, albuminuria,'any abnormality'.	Rise in systolic or diastolic BP of 30 resp. 15 mmHg (in seated position, Korotkoff phase V) ; or ≥300 mg proteinuria in 24 h; or generalized edema with one of the above.	Plasma Fn
Paarlberg[38] (1996)	Secondary / tertiary care (1)	The Netherlands	cohort	228	7.70	Singleton pregnancies,.normotensive <20 wks gest.	IDDM, CRD, APLS, age < 18; miscarriage before 16 wks; treatment; Crohn; idiopathic hyperglobulinuria; myomata uteri; uterine anomaly; sickle cell anemia; trisomy-21 infant; twin pregnancy; congenital abnormalities.	Diastolic BP 90 mmHg, rise in diastolic BP of 15 mmHg (in seated position, Korotkoff phase V); proteinuria of 0.3 g in 24 h.	Total plasma Fn
Sud[40] (1999)	Secondary / tertiary care (1)	India	cohort	100	14.0	Singleton pregnancies,.normotensive <20 wks gest.	DM, multiple pregnancies, history of: trauma, surgery, blood transfusion 6 mnths prior; disorders complicating pregnancy and coagulation disorders.	BP 140/90 mmHg on more than two occasions 6 h apart, proteinuria ≥0.3 gm/l in 24 h or 1+; pedal edema of 1+ after 12 hours of rest.	Plasma Fn
Islami[35] (2001)	Secondary / tertiary care (1)	Switzerland	cohort	198	4.50	Normotensives and hypertensives; some women were proteinuric < 20 wks gest; not al women were primigravid	No exclusion criteria; comorbidities classified in subgroups	Diastolic BP 90 mmHg on at leats two occasions and >0.3 g proteinuria/day.	ED-B Fn
Östlund[37] (2001)	Secondary / tertiary care (1)	Sweden*	cohort	228	2.60	Normotensive and non-proteinuric <20 wks gest.	NR	BP ≥140/90 mmHg and albumninuria ≥0.3 g/day or 2+ dipstick.	Total Plasma Fn
Chavarria[42] (2002)	Primary care (1)	Mexico	Nested and matched CC	78	6.88	Normotensive and non-proteinuric <20 wks gest.	IDDM, CRD, APLS, SLE, miscarriages, multiple pregnancies, essential hypertension, aspirin therapy, gest/transient hypertension, gest.DM, oligohydramnion, stillbirth, preterm delivery.	BP ≥ 140/90 mmHg, rise in systolic or diastolic BP of 30 resp. 15 mmHg (in sitting position, Kortokoff phase V), at least twice, ≥6 h apart; >300 mg proteinuria in 24 h or dipstick 1+; and edema 1+ after bed rest.	ED-B Fn
Madazli[41] (2005)	Secondary / tertiary care (1)	Turkey	cohort	122	11.5	Singleton pregnancies, normotensive and non-proteinuric; not all were primigravid.	NR	BP 140 / 90 mm Hg or greater, 6 h or more apart mmHg (in sitting position, Kortokoff phase V), and consistent proteinuria (300 mg/day or more).	Plasma Fn

*In the second column, in parentheses, the numbers of centers in which the study was conducted is stated. * = according to author's affiliation; ** = patients of which fibronectin levels were measured in first or second trimester. CC = case control; NR = not reported; PE = pre-eclampsia; wks gest = weeks gestation; (ID)DM = Insulin Dependent Diabetes Mellitus; BP = Blood pressure; Fn = fibronectin; h = hours; pp = post partum.*

care, except for one study, which was conducted in an unclear reported number of hospitals providing primary and secondary care[34]. Since several definitions of pre-eclampsia prevail worldwide, different reference standards were used. Three studies[39,40,42] included the presence of oedema in their definition of pre-eclampsia and one[45] included the presence of hyperuricaemia. The incidence of pre-eclampsia varied from 2.6% to 19.3% (median 7.7%), but in three studies the incidence in the studied population could not be extracted. Mean maternal ages varied from 19 to 31 years. Treatment with aspirin, other anti-inflammatory or anti-hypertensive drugs was only reported when treatment was one of the exclusion criteria. Two studies did not report any selection criteria[34,43]. In general, the reference test was described in sufficient detail, whereas the index test was not. Blind assessment of either the index test or the reference standard was also poorly reported. Figure 6.2 shows the assessed quality items.

6.3.2 Data analysis

Of the 12 studies included in the review, three studies reported the measurement of total plasma Fn[34,37,38], four measured cellular Fn[35,39,42,45] and one study measured both[44]. Although insufficient details were provided by three other studies, the results indicate that four of them measured total plasma Fn[36,39,41,45]. The twelve stud-

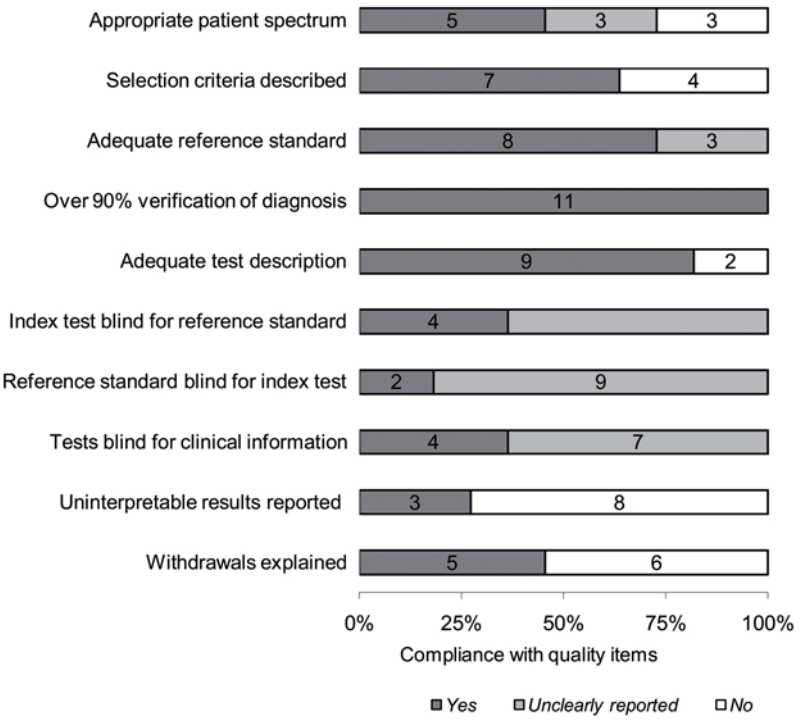

Figure 6.2. Methodological quality of included studies.
Data presented as 100% stacked bars, figures in the stacks represent number of studies.

ies all report assays that are based on immunological principles. Seven studies reported ELISA assays and five of those reported commercially available test kits. Three studies reported other commercially available tests and two reported only the immunologic principle.

Because two authors reported explicitly non-Normal distributions of the Fn-values and one other used non-parametric statistical analyses, we decided not to recalculate Normal distributions from mean and SDs in order to construct 2x2 tables that way. Thus, only five studies reported sufficient details to replicate 2x2 tables and to calculate measures of predictive accuracy[38,39,41-43]. These studies included a total of 573 pregnant women of whom 109 developed pre-eclampsia. One of those studies, Chavarria et al.[42], reported ROC-curves separately for Fn values in weeks 18 to 22 and in weeks 22 to 26. However, only for weeks 22 to 26, the results were also reported in a table. When we compared the values of the ROC curve with the values in the table (by labelling the depicted dots with the reported threshold values), the sensitivities reported in the table did not entirely match with the sensitivities reported in the figure. Therefore, the thresholds presented here may slightly differ from the original results. The results are listed in Table 6.2 and Figure 6.3.

Table 6.2 Measures of accuracy.

First Author	Fn fraction	Gest. Period	Threshold (µg/ml)	Sensitivity	Specificity	LR+	LR-
Lockwood[44]	ED 1+	1st trim	2.8	1.00	0.75	4.00	0.00
			3	0.67	0.75	2.67	0.44
			3.2	0.67	0.75	2.67	0.44
			3.4	0.67	0.75	2.67	0.44
			3.6	0.50	0.88	4.00	0.57
	ED 1+	2nd trim	3.9	0.85	0.74	3.26	0.20
			4.2	0.80	0.78	3.68	0.26
			4.6	0.55	0.83	3.16	0.54
			5	0.50	0.96	11.50	0.52
Chavarria[42]	ED-B Fn	2nd trim	3.5	0.74	0.72	2.64	0.36
			3.6	0.70	0.75	2.80	0.40
			3.7	0.64	0.82	3.56	0.44
			3.8	0.63	0.85	4.20	0.44
			3.9	0.56	0.88	4.67	0.50
Lockwood[44]	Total Fn	1st trim	347	0.83	0.63	2.22	0.27
			370	0.67	0.63	1.78	0.53
			393	0.50	0.75	2.00	0.67
Lockwood[44]	Total Fn	2nd trim	320	0.70	0.43	1.24	0.69
			350	0.55	0.74	2.11	0.61
Soltan[39]	Total Fn	14-24 wks	293.03	0.65	0.94	11.46	0.37
Paarlberg[38]	Total Fn	1st trim	240	0.52	0.64	1.47	0.74
		2nd trim	230	0.69	0.67	2.09	0.46
Madazli[41]	Total Fn	21-26 wks	370	0.64	0.86	4.57	0.42

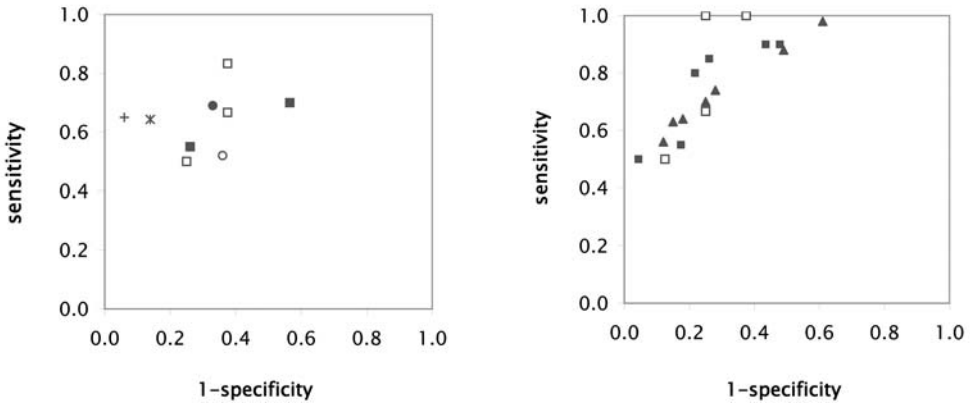

Figure 6.3. ROC plot of the cellular(a) and total(b) Fn assays at various thresholds.
Figure 6.3a. ROC plot of the cellular Fn assays at various thresholds. Depicted are the sensitivities and specificities of Lockwood et al. (□, first trimester and ■, second trimester) and Chavarria et al. (▲, second trimester). Sensitivities lower than 50% are not depicted. Figure 6.3b. ROC Plot of the total Fn assays. Depicted are the sensitivities and specificities of Lockwood et al. (□, first trimester and ■, second trimester), Soltan et al. (+, week 14-24), Paarlberg et al. (○, first trimester and ●, second trimester) and Madazli et al. (, week 21-26). The study of Lockwood et al. provided results at various thresholds. Sensitivities lower than 50% are not depicted.*

The sensitivities of all Fn assays vary widely, depending on the chosen threshold (Table 6.2). Requiring a sensitivity of at least 50%, the specificity achieved with the cellular Fn assays ranged from 72% to 96%. For the total Fn assays these specificities ranged from 43% to 94%. The positive Likelihood Ratios ranged from 1.64 to 11.5 for the cellular Fn assays and from 1.24 to 10.8 for the total Fn assays. A Likelihood Ratio of 4.67 would increase a pre-test probability to develop pre-eclampsia of 5% to a post-test probability of 20%. The negative Likelihood Ratios varied from 0.0 to 0.57 for the cellular Fn assays and from 0.27 to 0.74 for the total Fn assays. This implies that a negative cellular Fn test result may decrease a pre-test probability of 5% to a post-test probability that approximates 0. Figure 6.3a and 6.3b show the ROC plots. Figure 6.3a only shows the results of the cellular Fn assays. These seem to allow a summary ROC curve. However, these two studies measured different types of cellular Fn (ED-A versus ED-B), assessed first and second trimester and Lockwood et al. did not report on the type of assay used. Therefore, we decided not to draw a summary ROC curve or calculate pooled estimates. Figure 6.3b shows the sensitivities and specificities of the total Fn assays. These studies were also methodologically and clinically heterogeneous; hence we did not calculate pooled estimates here either.

6.4 Discussion

On reviewing 12 studies and analysing five, we found that the accuracy of plasma determination of Fn before the 25th (mean) gestational week to predict pre-eclampsia appears to vary widely among the studies. Because a Normal distribution of Fn-levels could not be assumed, the conclusions are based on only five studies. The exclusion of the other seven studies, that included a total of 791 women, reduced the statistical power of this review. Unfortunately, the extent to which its main conclusions are affected remains speculative. The included studies differed from each other in several aspects, for example, for study design, Fn fraction measured, cut-off values used to determine positive results, incidence of pre-eclampsia, and country where the study was conducted. Furthermore, reference standards (the criteria for pre-eclampsia) varied over the studies as well. None of these five studies reported about blinding of the reference test, whereas the index test is only well described (with manufacturer and inter- and intra-assay variations) by Chavarria and co-workers[42]. These characteristics may artificially inflate or reduce the true sensitivities and specificities[31,46]. We were unable to analyse the effects of these biases and variations in this review due to the limited number of primary studies yielding usable results. Lockwood et al.'s study[44] contains some direct evidence that measurement of cellular Fn is more informative than that of total Fn. This study does not indicate that measurement of (cellular) Fn in the 2nd trimester is more useful than in the 1st trimester.

Earlier reviews about the prediction of pre-eclampsia that also included Fn measurements[17-26] report conflicting results and did not always differentiate between cellular and total Fn. Conde-Agudelo and colleagues reviewed methods for prediction and screening of pre-eclampsia twice[17,18]. The conclusion in the first review was based on three studies and in the second review on one study. In addition, this review has been criticized for performing the crucial steps of screening of bibliographies and data-extraction using a single reviewer only and suboptimal statistical methods[27].

Because the results of the cellular Fn assays on average seem to have a slightly better performance than the total Fn assays, we think that further research should focus on the use of cellular Fn for the prediction of pre-eclampsia. Such studies should report according to the STARD recommendations for diagnostic accuracy studies[47]. In particular, more details on blinding, concomitant treatment, entry criteria, and the exact Fn technology used is important to readers and reviewers alike. Furthermore, added value of Fn determination given patient information, such as history items, available at the time of assay is an important issue and usually requires multivariable analysis[50].

At this point, it is not yet possible to advise clinicians on the optimal threshold to achieve a particular specificity in their daily practice. However, this review shows that when both sensitivity and specificity are not allowed to drop below 50%, the

cellular assays can be used to exclude women who are not likely to develop pre-eclampsia from further follow up for the disease (see the low negative Likelihood ratio). On the other hand, formal decision analysis is needed to specify the role of Fn tests as add-ons to clinical information that may usually be available at the point of Fn test ordering decision. For example to answer the question whether it is useful to prescribe preventive drugs to a woman that tested positive.

In conclusion, based on the limited evidence available, the determination of plasma levels of especially cellular Fn seems to be a promising tool to predict pregnant women's risk of pre-eclampsia. Determination of total Fn appears to give a larger variation in results. However, more well-designed and adequately reported studies are necessary to populate ultimate decision-analytic models.

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