

Appendix 3: Characteristics of studies of uterine artery Doppler ultrasonography used to predict pre-eclampsia in patients at low risk or unspecified risk (Appendix 3A) and in patients at high risk (Appendix 3B)

Appendix 3A: Patients at low risk or unspecified risk of pre-eclampsia (part 1 of 9)									
Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff point, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)	
Aardema et al, ¹ the Netherlands	21-22	531 (0.9)	Healthy, nulliparous women	Diastolic pressure \geq 90 mm Hg twice; proteinuria = dipstick \geq 2+ (International Society for the Study of Hypertension in Pregnancy criteria ⁷⁵)	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Notch index > 0.03 • Pulsatility index > 1.3 	<ul style="list-style-type: none"> • 0/5 • 0/5 	<ul style="list-style-type: none"> • 395/526 • 410/526 	
Albaiges et al, ² United Kingdom	22-25	1 757 (3.7)	Women with singleton pregnancy receiving routine antenatal care	Blood pressure \geq 140/90 mm Hg twice, at least 2 h apart; proteinuria \geq 0.3 g of protein in 24-h urine collection or dipstick 0.3 g/L	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Bilateral notching or mean pulsatility index > 1.45 	• 29/65	• 1592/1692	
						<ul style="list-style-type: none"> • Bilateral notching 	• 21/65	• 1636/1692	
						<ul style="list-style-type: none"> • Mean pulsatility index > 1.45 	• 23/65	• 1624/1692	
						<ul style="list-style-type: none"> • Bilateral notching and mean pulsatility index > 1.45 	• 15/65	• 1668/1692	
Antsaklis et al, ³ Greece	19-21 24	675 (3.1)	Nulliparous women. Excluded: women with multiple pregnancy, renal or cardiovascular disease, diabetes mellitus, or fetal abnormalities	Blood pressure \geq 140/90 mm Hg twice, 6 h apart; proteinuria = \geq 0.3 g of protein in 24-h urine collection	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Any notching 	• 17/21	• 552/654	
						<ul style="list-style-type: none"> • Bilateral notching 	• 10/21	• 607/654	
						<ul style="list-style-type: none"> • Unilateral notching 	• 7/21	• 578/654	
						<ul style="list-style-type: none"> • Any notching 	• 16/21	• 602/654	
						<ul style="list-style-type: none"> • Bilateral notching 	• 9/21	• 623/654	
						<ul style="list-style-type: none"> • Unilateral notching 	• 7/21	• 612/654	
Aquilina et al, ⁴ United Kingdom	18-22	640 (5.5)	Women with unspecified risk factors who had inhibin A measurement. Excluded: women with multiple pregnancy, diabetes mellitus, hypertension < 20 wk gestation, or chromosome or structural anomalies	Diastolic pressure \geq 90 mm Hg twice, > 4 h apart, or \geq 110 mm Hg once; proteinuria = > 0.3 g protein in 24-h urine collection or dipstick \geq 2+ twice, 4 h apart; no urinary tract infection (Davey and MacGillivray criteria ⁷⁶)	Transabdominal, colour + pulsed wave, unreported site	Bilateral notching and mean resistance index \geq 0.55, or unilateral notching and mean resistance index \geq 0.65	21/35	563/605	
Aquilina et al, ⁵ United Kingdom	18-22	550 (7.3)	Primiparous women with unspecified risk factors receiving routine antenatal care	Diastolic pressure \geq 90 mm Hg twice, > 4 h apart, or \geq 110 mm Hg once; proteinuria \geq 0.3 g protein in 24-h urine collection or dipstick \geq 2+ twice without urinary tract infection (Davey and MacGillivray criteria ⁷⁶)	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Resistance index • A/C ratio • S/D ratio 	<ul style="list-style-type: none"> • 35/40 • 34/40 • 31/40 	<ul style="list-style-type: none"> • 332/510 • 342/510 • 332/510 	

continued

Appendix 3A: Patients at low risk or unspecified risk of pre-eclampsia (part 2 of 9)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff point, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Arenas et al, ⁶ Spain	20	319 (3.5)	Women with unspecified risk factors. Excluded: those with multiple pregnancy or fetal anomalies	Blood pressure \geq 140/90 mm Hg, proteinuria = $>$ 0.3 g protein in 24-h urine collection	Transabdominal, colour + pulsed wave, crossover	Resistance index \geq 0.59	8/11	227/308
Audibert et al, ⁷ France	18-26	2 615 (2.0)	Women who had α -fetoprotein and human chorionic gonadotropin testing at 14-18 wk, and ultrasound screening. Excluded: women without ultrasound screening at 10-14 wk for dating, women with raised nuchal translucency, no Doppler ultrasound at 18-26 wk, delivery $<$ 24 wk	Systolic pressure \geq 140 mm Hg or diastolic pressure \geq 90 mm Hg twice; proteinuria = $>$ 0.3 g protein in 24-h urine collection or dipstick 2+ (also definition for severe pre-eclampsia)	Unreported route, type and site	<ul style="list-style-type: none"> • Bilateral notching • Unilateral notching 	<ul style="list-style-type: none"> • 11/51 • 20/51 	<ul style="list-style-type: none"> • 2460/2564 • 2265/2564
Ay et al, ⁸ Turkey	24-26	178 (7.9)	Women attending for Down syndrome serum screening. Excluded: women with multiple pregnancy, hypertension $<$ 26 wk, diabetes mellitus, fetal anomalies, previous pre-eclampsia	Blood pressure \geq 140/90 mm Hg $>$ 20 wk; proteinuria = \geq 0.3 g protein in 24-h urine collection	Transabdominal, unreported type, crossover	<ul style="list-style-type: none"> • Any notching • Any notching or high resistance index 	<ul style="list-style-type: none"> • 12/14 • 12/14 	<ul style="list-style-type: none"> • 160/164 • 142/164
Bassim et al, ⁹ Germany	20-24	490 (2.9)	Routine screening	Systolic pressure \geq 140 mm Hg or diastolic pressure \geq 90 mm Hg twice, 6 h apart; proteinuria = \geq 0.3 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Bilateral notching	5/14	445/476
Bower et al, ¹⁰ United Kingdom	18-22	2 058 (0.3)	Women with unspecified risk factors. Excluded: women with multiple pregnancy, gestational age outside study limits, fetal anomalies	<p>Mild pre-eclampsia: blood pressure elevated by $<$ 30/25 mm Hg; proteinuria = dipstick 1+</p> <p>Moderate pre-eclampsia: blood pressure elevated by $<$ 30/25 mm Hg; proteinuria = dipstick \geq 2+</p> <p>Severe pre-eclampsia: diastolic pressure \geq 110 mm Hg and increase in blood pressure \geq 30/25 mm Hg; proteinuria = dipstick \geq 2+, or \geq 0.5 g protein in 24-h urine collection</p>	Transabdominal, colour wave, crossover	<p>Resistance index $>$ 95th centile or any notching</p> <ul style="list-style-type: none"> • Mild pre-eclampsia • Moderate pre-eclampsia • Severe pre-eclampsia 	<ul style="list-style-type: none"> • 2/7 • 14/16 • 23/29 	<ul style="list-style-type: none"> • 1724/2051 • 1727/2051 • 1723/2051

continued

Appendix 3A: Patients at low risk or unspecified risk of pre-eclampsia (part 3 of 9)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff point, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Bower et al, ¹¹ United Kingdom	18-22 24	2 058 (2.2) 2 026 (2.2)	Women with unspecified risk factors	Mild pre-eclampsia: blood pressure elevated by < 30/25 mm Hg; proteinuria = dipstick 1+ Moderate pre-eclampsia: blood pressure elevated by < 30/25 mm Hg; proteinuria = dipstick ≥ 2+ Severe pre-eclampsia: diastolic pressure ≥ 110 mm Hg and increase in blood pressure ≥ 30/25 mm Hg; proteinuria = dipstick ≥ 2+, or ≥ 0.5 g protein in 24-h urine collection	Transabdominal, colour wave, crossover	Unilateral notching • Gestation 18-22 wk • Gestation 24 wk	• 37/45 • 35/45	• 1749/2013 • 1902/1981
Caforio et al, ¹² Italy	18-20 22-24	530 (0.6)	Healthy nulliparous women. Excluded: women with multiple pregnancy, fetal anomalies, chromosomal abnormalities, infections, Rhesus isoimmunization, nonimmune hydrops, preterm prelabour rupture of membranes, intrauterine stillbirth, delivery < 26 wk	Davey and McGillivray criteria ⁷⁶	Unreported route, colour + pulsed wave, crossover	Resistance index > 90th centile • Gestation 18-20 wk • Gestation 22-24 wk	• 3/3 • 3/3	• 369/527 • 395/527
Campbell et al, ¹³ United Kingdom	19-21 24-26	264 (4.9)	Not reported	Blood pressure ≥ 140/90 mm Hg at least twice, 4 h apart; proteinuria = ≥ 0.3 g protein in 24-h urine collection or dipstick ≥ 1+	Unreported route and site, colour + continuous wave	Any notching or RI > 0.6 • Gestation 19-21 wk • Gestation 24-26 wk	• 13/13 • 13/13	• 99/251 • 173/251
Carbillon et al, ¹⁴ France	12-14 22-24	243 (4.9)	Women receiving routine ultrasound screening	Blood pressure ≥ 140/90 mm Hg twice, 4 h apart; proteinuria = ≥ 0.3 g protein in 24-h urine collection or dipstick 1+	Transabdominal, unreported type, ascending branch	• Any notching (v. no notching) • Bilateral notching	• 10/12 • 5/12	• 102/231 • 215/231
Driul et al, ¹⁵ Italy	24	840 (1.2)	Not reported	Not specified	Unreported route, colour, crossover	Monolateral notching or resistance index > 0.60	4/10	723/830
Frusca et al, ¹⁶ Italy	24	419 (1.9)	Nulliparous women without risk factors for pre-eclampsia. Excluded: women with chronic hypertension, diabetes mellitus or autoimmune disease	Blood pressure > 140/90 mm Hg twice, 4 h apart; proteinuria = > 0.3 g protein in 24-h urine collection (Davey and MacGillivray criteria ⁷⁶)	Unreported route, colour + pulsed wave, crossover	• Resistance index > 0.58 • Resistance index > 0.58 and notching	• 4/8 • 4/4	• 379/411 • 18/32

continued

Appendix 3A: Patients at low risk or unspecified risk of pre-eclampsia (part 4 of 9)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff point, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Geipel et al, ¹⁷ Germany	18-24	114 (9.6)	Women with singleton pregnancy (control group of intracytoplasmic sperm injection)	Blood pressure \geq 140/90 mm Hg repeated; proteinuria = \geq 0.5 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Bilateral notching	8/11	87/103
Gomez et al, ¹⁸ Spain	11-14	999 (2.2)	Women with singleton pregnancy attending for routine antenatal care. Excluded: cases of fetal anomalies, and women given ASA, heparin or antihypertensive medication before enrolment	According to International Society for the Study of Hypertension in Pregnancy criteria ⁷⁵	Unreported route, colour + pulsed wave, crossover	Pulsatility index > 95th centile	5/22	929/977
Hafner et al, ¹⁹ Austria	21-23	2 489 (1.0)	All women with singleton pregnancy	Blood pressure > 140/90 mm Hg twice or > 155/105 mm Hg once or need for antihypertensive therapy; proteinuria = dipstick 2+ twice or 30 mg protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Bilateral notching	3/25	2241/2464
						Mean pulsatility index > 90th centile	7/25	2220/2464
Harrington et al, ²⁰ United Kingdom	19-21	458 (9.0)	Multiparous women with unspecified risk factors who had singleton pregnancy. Excluded: cases of fetal anomalies	Diastolic pressure \geq 90 mm Hg twice, 4 h apart, or \geq 110 mm Hg once; proteinuria = > 0.3 g protein in 24-h urine collection or dipstick 2+ twice, 4 h apart, no urinary tract infection	Unreported route, colour + pulsed wave, crossover	Bilateral notching plus mean resistance index \geq 0.55 (50th centile), or unilateral notching plus mean resistance index \geq 0.65 (80th centile)	1/2	416/456
Harrington et al, ²¹ United Kingdom	12-16	626 (4.8)	Women with unspecified risk factors who had singleton pregnancy	Systolic pressure \geq 140 mm Hg or diastolic pressure \geq 90 mm Hg; proteinuria = > 0.3 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Bilateral notching (v. unilateral or no notching)	• 27/30	• 418/596
						Any notching	• 29/30	• 277/596
Harrington et al, ²² United Kingdom	18-21	1 204 (3.7)	Women with unspecified risk factors. Excluded: women with multiple pregnancy, fetal anomalies, women with pre-eclampsia or fetal growth restriction \leq 24 wk	Blood pressure elevated by \geq 30/25 mm Hg twice, 4 h apart, or diastolic pressure \geq 110 mm Hg; proteinuria = 0.5 g in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Any notching or resistance index > 95th centile	• 34/44	• 1084/1160
						Bilateral notching	• 24/44	• 1136/1160
						Unilateral notching	• 10/44	• 1108/1160
Harrington et al, ²³ United Kingdom	20	2 437 (2.0)	Women with unspecified risk factors	Baseline diastolic pressure < 90 mm Hg and subsequent increase of \geq 25 mm Hg twice, 4 h apart; proteinuria = > 0.5 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Resistance index > 95th centile or notching	38/48	2037/2389

continued

Appendix 3A: Patients at low risk or unspecified risk of pre-eclampsia (part 5 of 9)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff point, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Kurdi et al, ²⁴ United Kingdom	19-21	946 (2.2)	Women with unspecified risk factors. Excluded: women with multiple pregnancy, fetal anomalies, women already receiving low-dose ASA	Baseline diastolic pressure < 90 mm Hg and subsequent increase of \geq 25 mm Hg; if baseline diastolic pressure \geq 90 mm Hg, then increase of 15 mm Hg; proteinuria = dipstick \geq 1+, no urinary tract infection	Unreported route, colour + pulsed wave, crossover	• Bilateral notching plus mean resistance index > 0.55 (50th centile) or unilateral notching plus mean resistance index > 0.65 (90th centile) or mean resistance index > 0.7 (95th centile)	• 15/21	• 724/925
						• Bilateral notching	• 13/21	• 821/925
Madazli et al, ²⁵ Turkey	21-26	122 (11.5)	Normotensive women	Blood pressure \geq 140/90 mm Hg twice, 6 h apart; proteinuria = \geq 0.3 g protein in 24-h urine collection Severe pre-eclampsia: blood pressure \geq 160/110 mm Hg twice, 6 h apart; proteinuria = dipstick 3+, oliguria, other signs and symptoms	Unreported route, colour + pulsed wave, crossover	• Mean S/D ratio > 2.6 (2 SD) • Mean S/D ratio > 2.6 (2 SD) – severe pre-eclampsia	• 10/14 • 5/5	• 84/108 • 8/117
Marchesoni et al, ²⁶ Italy	20, 24	900 (2.9)	Women with unspecified risk factors	Blood pressure > 140/90 mm Hg; proteinuria = > 0.3 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	• Bilateral notching • Any notching	• 16/26 • 20/26	• 830/874 • 723/874
Martin et al, ²⁷ United Kingdom	11-14	3 045 (2.1)	Women receiving routine antenatal care	Diastolic pressure \geq 90 mm Hg twice > 4 h apart, proteinuria \geq 0.3 g protein in 24-h urine collection or dipstick \geq 2+ twice midstream urine if no 24-h collection available (International Society for the Study of Hypertension in Pregnancy criteria ²⁹)	Unreported route, colour + pulsed wave, crossover	Pulsatility index > 2.35 (95th centile)	17/63	2844/3099
Mires et al, ²⁸ United Kingdom	18-20	6 579 (5.5)	All women with singleton pregnancy	ICD-9 classification	Unreported route, colour + pulsed wave, crossover	Bilateral notching	• 23/363 • 8/363	• 6131/6216 • 6192/6216
	22-24					• Gestation 18-20 wk • Gestation 22-24 wk		
Morris et al, ²⁹ Australia	18	768 (4.7)	All nulliparous women, 102 women with abnormal Doppler result randomly assigned to receive ASA or placebo (randomized controlled trial)	Blood pressure > 140/90 mm Hg with rise in diastolic pressure \geq 15 mm Hg twice 6 h apart, proteinuria dipstick 1+ twice 6 h apart or hyperuricemia	Unreported route, colour + pulsed wave, crossover	S/D > 3.3 (+ 2 SD) or unilateral notching + S/D > 3.0 (90th centile)	8/36	665/732

continued

Appendix 3A: Patients at low risk or unspecified risk of pre-eclampsia (part 6 of 9)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff point, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Nicolaides et al, ³⁰ United Kingdom	11-13.6	433 (2.3)	Women being screened for Down syndrome (nested case-control study)	According to International Society for the Study of Hypertension in Pregnancy criteria ⁷⁵	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Pulsatility index: 90% detection rate • Pulsatility index: 10% false-positive rate 	<ul style="list-style-type: none"> • 9/10 • 4/10 	<ul style="list-style-type: none"> • 292/423 • 381/423
North et al, ³¹ Australia	19-24	446 (3.4)	Healthy nulliparous women. Excluded: women with renal disease or diabetes mellitus	Blood pressure \geq 140/90 mm Hg and rise in diastolic blood pressure \geq 15 mm Hg twice 4 h apart, proteinuria > 0.3 g protein in 24-h urine collection or dipstick \geq 2+	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Resistance index > 90th centile • A/C ratio > 90th centile • Resistance index > 0.53 • Resistance index > 0.54 • Resistance index > 0.55 • Resistance index > 0.56 • Resistance index > 0.57 	<ul style="list-style-type: none"> • 4/15 • 8/15 • 8/15 • 7/15 • 7/15 • 5/15 • 4/15 	<ul style="list-style-type: none"> • 382/431 • 381/431 • 341/431 • 353/431 • 367/431 • 379/431 • 387/431
Ohkuchi et al, ³² Japan	16-23.9	288 (3.1)	Healthy women with unspecified risk factors who had singleton pregnancy	Diastolic blood pressure \geq 90 mm Hg twice 4 h apart, proteinuria \geq 0.3 g protein in 24-h urine collection or dipstick \geq 2+ (Davey and MacGillivray criteria ⁷⁶)	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Any notching • Bilateral notching • Resistance index > 91st centile • A/C ratio > 91st centile • Notch depth index > 0.14 	<ul style="list-style-type: none"> • 6/9 • 5/9 • 6/9 • 7/9 • 6/9 	<ul style="list-style-type: none"> • 226/279 • 256/279 • 236/279 • 242/279 • 258/279
Onalan et al, ³³ Turkey	19-21	406 (7.9)	Women \leq 40 yr who had fasting total serum homocysteine level measured. Excluded: women with multiple pregnancy, history of pre-eclampsia, hypertension < 20 wk, altered renal function, diabetes mellitus, chronic disease or fetal anomalies, and women who used folic acid > 12 wk, had special folate diet or were prescribed antifolate drugs	Diastolic blood pressure \geq 90 mm Hg twice 4 h apart, proteinuria \geq 0.3 g protein in 24-h urine collection, no urinary tract infection (Davey and MacGillivray criteria ⁷⁶)	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Bilateral notching + mean resistance index > 0.55 (50th centile), all unilateral notching + mean resistance index > 0.65 (80th centile), or any notching + mean resistance index > 0.7 (95th centile) • Unilateral notching • Bilateral notching • Any notching 	<ul style="list-style-type: none"> • 14/32 • 8/32 • 7/32 • 15/32 	<ul style="list-style-type: none"> • 347/374 • 320/374 • 339/374 • 285/374
Papageorgiou et al, ³⁴ United Kingdom, Brazil, Chile, South Africa	22-24	16 806 (2.2)	Women with unspecified risk factors who had singleton pregnancy	Diastolic blood pressure \geq 90 mm Hg twice 4 h apart, proteinuria > 0.3 g protein in 24-h urine collection or dipstick \geq 2+ twice (International Society for the Study of Hypertension in Pregnancy criteria ⁷⁵)	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Bilateral notching • Pulsatility index > 1.44 • Pulsatility index > 1.6 or bilateral notching • Pulsatility index > 1.38 	<ul style="list-style-type: none"> • 124/369 • 168/369 • 177/369 • 179/369 	<ul style="list-style-type: none"> • 14 886/16 437 • 14 960/16 437 • 14 518/16 437 • 14 518/16 437

continued

Appendix 3A: Patients at low risk or unspecified risk of pre-eclampsia (part 7 of 9)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff point, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Park et al, ³⁵ Korea	20-24	1 090 (1.7)	Low-risk women. Excluded: women with multiple pregnancy, cardiovascular or renal disease, diabetes mellitus, fetal anomalies, intrauterine growth restriction, pregnancy-induced hypertension, preterm labour before performance of Doppler ultrasonography	Blood pressure \geq 140/90 mm Hg twice 6 h apart, proteinuria > 0.3 g protein in 24-h urine collection or dipstick \geq 1+	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> Any notching Unilateral notching Bilateral notching 	<ul style="list-style-type: none"> • 17/18 • 7/18 • 10/18 	<ul style="list-style-type: none"> • 824/1 072 • 883/1 072 • 1 013/1 072
Parra et al, ³⁶ Chile	11-14 22-25	922 (4.4)	Asymptomatic women using antioxidant vitamins	Blood pressure \geq 140/90 mm Hg twice 6 h apart, proteinuria > 0.3 g protein in 24-h urine collection or dipstick \geq 1+ twice 6 h apart	Unreported route, colour + pulsed wave, crossover	• Pulsatility index > 95th centile (2.43)	• 8/33	• 846/889
						• Pulsatility index > 95th centile (1.54)	• 16/33	• 851/889
Phupong et al, ³⁷ Thailand	22-28 (24.9 \pm 1.9)	322 (5.9)	Healthy nulliparous and multiparous women. Excluded: women with multiple pregnancy, cardiovascular or renal disease, diabetes mellitus, fetal anomalies	Blood pressure > 140/90 mm Hg twice 6 h apart, proteinuria \geq 0.3 g protein in 24-h urine collection or dipstick 1+ Severe pre-eclampsia: Blood pressure \geq 110 mm Hg, proteinuria 5 g protein in 24-h urine collection or dipstick 3+	Unreported route, colour + pulsed wave, crossover	Any notching	7/19	252/303
Prefumo et al, ³⁸ United Kingdom	18-23	4 149 (0.4)	All singleton live births from clinical database. Excluded: fetal anomalies. Outcome measures: severe pre-eclampsia, delivery < 32 wk	Blood pressure > 140/90 mm Hg, proteinuria \geq 0.3 g protein in 24-h urine collection or dipstick 1+ twice if no 24-h urine collection available	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> Bilateral notching Any notching 	<ul style="list-style-type: none"> • 11/17 • 13/17 	<ul style="list-style-type: none"> • 3933/4132 • 3498/4132
Sato et al, ³⁹ Japan	16-23	333 (4.8)	Women at low risk for pre-eclampsia	Gestose Index 2	Unreported route, colour + pulsed wave, crossover	• Pulsatility index \geq 1.20	• 13/16	• 228/317
		341 (4.7)				• Resistance index > 0.60	• 12/16	• 219/317
Schwarze et al, ⁴⁰ Germany	19-22 and 23-26	346 (4.9)	Women with singleton pregnancy. Excluded: women with multiple pregnancy, essential hypertension, diabetes mellitus, autoimmune disease, history of pre-eclampsia, intrauterine growth restriction, intrauterine stillbirth, placental abruption in previous pregnancies, fetal anomalies	Blood pressure \geq 140/90 mm Hg, proteinuria \geq 0.3 g protein in 24-h urine collection, no urinary tract infection	Unreported route, colour + pulsed wave, crossover	• Any resistance index > 0.58	• 14/17	• 208/329
						• Both resistance indices > 0.58	• 7/17	• 284/329
						• Any resistance index > 0.7	• 7/17	• 289/329
						• Both resistance indices > 0.7	• 3/17	• 325/329
						• Any notching	• 14/17	• 198/329
• Bilateral notching	• 8/17	• 273/329						

continued

Appendix 3A: Patients at low risk or unspecified risk of pre-eclampsia (part 8 of 9)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff point, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Soutif et al, ⁴¹ France	21, 24	315 (1.3)	Primiparous women. Excluded: women with nephropathy, chronic hypertension, diabetes mellitus, systemic disorder, multiple pregnancy	Systolic blood pressure \geq 150 mm Hg or diastolic blood pressure \geq 90 mm Hg twice, proteinuria \geq 1.0 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	S/D ratio > 2.6 on either side or unilateral notching	3/4	264/311
Subtil et al, ⁴² France, Belgium	22-24	1 170 (2.1)	Women undergoing routine Doppler examination given either ASA or placebo if abnormal findings (randomized controlled trial)	Pregnancy induced hypertension not quantified, proteinuria dipstick 2+ or protein \geq 0.5 g/L in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Resistance index > 0.61 or any notching	14/24	923/1146
Tranquilli et al, ⁴³ Italy	24	75 (18.7)	Normotensive primigravid women. Excluded: primigravidous women with chronic hypertension, fetal anomalies, intrauterine growth restriction	Hypertension and proteinuria not quantified	Unreported route, colour + pulsed wave, crossover	Resistance index > 0.58	8/14	31/61
Uludag et al, ⁴⁴ Turkey	18-20	80 (12.5)	Women who were nonsmokers. Excluded: women with multiple pregnancy, diabetes mellitus, fetal anomalies	Blood pressure > 140/90 mm Hg > 24 wk or proteinuria > 0.3 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Bilateral notching	9/10	62/70
Valensise et al, ⁴⁶ Italy	24	192 (4.7)	Low-risk women ($n = 104$): primiparous, no current or previous relevant medical history. High-risk women ($n = 88$): history of pregnancy-induced hypertension, intrauterine growth restriction or intrauterine stillbirth. Excluded: women with intrauterine growth restriction detected on ultrasound screening or oligohydramnios	Gestational hypertension (Davey and MacGillivray criteria ⁷⁶), proteinuria > 0.3 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Resistance index > 0.58	8/9	152/183
Valensise et al, ⁴⁷ Italy	22 and 24	272 (3.3)	Primigravid women. Excluded: women with history of hypertension, diabetes mellitus, systemic lupus erythematosus, pharmacologic induction of ovulation, fetal or chromosomal anomalies	Davey and MacGillivray criteria, ⁷⁶ proteinuria: protein > 0.3 g/L in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Resistance index > 0.58 at 24 wk	8/9	245/263

continued

Appendix 3A: Patients at low risk or unspecified risk of pre-eclampsia (part 9 of 9)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff point, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Yu et al, ⁴⁸ United Kingdom	22-24	15 392 (2.0)	Women with unspecified risk factors who had low-risk singleton pregnancy	Diastolic blood pressure \geq 90 mm Hg twice 4 h apart, proteinuria \geq 0.3 g protein in 24-h urine collection or dipstick 2+	Unreported route, colour + pulsed wave, crossover	Pre-eclampsia overall <ul style="list-style-type: none"> • Pulsatility index: 2% false-positive ratio • Pulsatility index: 5% false-positive ratio (> 1.6) • Pulsatility index: 10% false-positive ratio Pre-eclampsia < 34 wk <ul style="list-style-type: none"> • Pulsatility index: 2% false-positive ratio • Pulsatility index: 5% false-positive ratio (> 1.6) • Pulsatility index: 10% false-positive ratio Pre-eclampsia > 34 wk <ul style="list-style-type: none"> • Pulsatility index: 2% false-positive ratio • Pulsatility index: 5% false-positive ratio (> 1.6) • Pulsatility index: 10% false-positive ratio 	<ul style="list-style-type: none"> • 87/297 • 127/297 • 153/297 • 43/297 • 56/297 • 61/297 • 44/297 • 74/297 • 95/297 	<ul style="list-style-type: none"> • 14 763/15 095 • 14 340/15 095 • 13 555/15 095 • 15 014/15 095 • 14 554/15 095 • 13 773/15 095 • 14 864/15 095 • 14 409/15 095 • 13 650/15 095
Zimmerman et al, ⁴⁹ Finland	22-24	55 (10.9)	High-risk women (n = 26): family or personal history of pre-eclampsia, chronic hypertension or intrauterine growth restriction or intrauterine stillbirth; 13 received ASA. Low-risk women (n = 29) (randomized controlled trial)	Blood pressure \geq 145/85 mm Hg, proteinuria (not specified, dipstick testing) on \geq 2 occasions 24 h apart; severe pre-eclampsia: blood pressure > 160/100 mm Hg	Unreported route, colour + pulsed wave, crossover	Bilateral notching only	6/6	25/49

Note: A/C ratio = ratio of peak systolic to early diastolic velocity, ASA = acetylsalicylic acid, FN = false negative, FP = false positive, S/D ratio = ratio of peak systolic to late diastolic velocity, SD = standard deviation, TN = true negative, TP = true positive.
 *Cohort study unless stated otherwise.

See next page for start of Appendix 3B; see end of document for references.

Appendix 3B: Patients at high risk for pre-eclampsia (part 1 of 6)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Aardema et al, ¹ the Netherlands	21-22	94 (7.5)	Multiparous women with singleton pregnancy who had history of hypertensive disorders in previous pregnancies but no current pathology	Diastolic blood pressure \geq 90 mm Hg twice, proteinuria = dipstick \geq 2+ (International Society for the Study of Hypertension in Pregnancy criteria ⁷⁵)	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Notch index > 0.03 • Pulsatility index > 1.3 	<ul style="list-style-type: none"> • 1/7 • 1/7 	<ul style="list-style-type: none"> • 70/87 • 59/87
Aardema et al, ⁵⁰ the Netherlands	21-22	94 (7.5)	Women with singleton pregnancy who had history of hypertensive disorders in previous pregnancies but no current pathology	Diastolic blood pressure \geq 90 mm Hg twice, proteinuria = dipstick \geq 2+	Unreported route, colour + pulsed wave, crossover	Any notching	1/7	70/87
Alkazaleh et al, ⁵¹ Canada	19-23	50 (26.0)	Women with α -fetoprotein > 2.0 multiples of the median and human chorionic gonadotropin level > 2.5 multiples of the median	American College of Obstetricians and Gynecologists criteria ⁷⁷	Unreported route, colour + pulsed wave, crossover	Mean pulsatility index > 1.45	9/11	18/37
Axt-Fliedner et al, ⁵² Germany	19-26	52 (7.7)	High-risk singleton pregnancies: history of pre-eclampsia, fetal growth restriction, intrauterine demise, abruption	Blood pressure \geq 140/90 mm Hg, proteinuria \geq 0.3 g protein in 24-h urine collection, no urinary tract infection	Transabdominal, colour, crossover	<ul style="list-style-type: none"> • Any resistance index > 0.58 • Both resistance indices > 0.58 • Any resistance index > 0.7 • Both resistance indexes > 0.7 • Bilateral notching • Any notching 	<ul style="list-style-type: none"> • 2/4 • 2/4 • 1/4 • 1/4 • 1/4 • 3/4 	<ul style="list-style-type: none"> • 19/48 • 36/48 • 42/48 • 46/48 • 34/48 • 23/48
Caforio et al, ¹² Italy	18-20	335 (12.5)	Women with chronic hypertension, diabetes mellitus, autoimmune disease, systemic lupus erythematosus, renal disease; history of stillbirths, intrauterine growth restriction, pre-eclampsia, habitual abortion	Davey and MacGillivray criteria ⁷⁶	Unreported route, colour + pulsed wave, crossover	Resistance index > 90th centile	39/42	202/301
Caruso et al, ⁵³ Italy	23-24	42 (21.4)	Women with chronic hypertension, singleton pregnancy. Excluded: women with autoimmune disease, fetal anomalies, Rhesus isoimmunization	Systolic blood pressure \geq 140 mm Hg or diastolic blood pressure \geq 90 mm Hg and exacerbation of hypertension, proteinuria > 0.3 g/L or dipstick > 1+ in 2 random samples or \geq 0.3 g protein in 24-h urine collection, no urinary tract infection	Transabdominal, colour, crossover	Resistance index > 90th centile	9/9	27/33
Caruso et al, ⁵⁴ Italy	18-24	28 (17.9)	Women with antiphospholipid syndrome	Davey and MacGillivray criteria ⁷⁶	Transabdominal, colour, crossover	Resistance index > 90th centile	4/5	18/23

continued

Appendix 3B: Patients at high risk for pre-eclampsia (part 2 of 6)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Chan et al, ⁵⁵ Hong Kong	20	334 (6.9)	High-risk women (age > 35 yr, poor obstetric history, medical complications of pregnancy, low pre-pregnancy weight, single mother, smoker > 10 cigarettes/d)	Blood pressure \geq 140/90 mm Hg twice, 6 h apart; proteinuria > 0.3 g protein in 24-h urine collection or dipstick \geq 2+	Unreported route and site, colour Doppler	<ul style="list-style-type: none"> Resistance index > 95th centile Resistance index > 90th centile + bilateral notching 	<ul style="list-style-type: none"> 4/23 5/23 	<ul style="list-style-type: none"> 297/311 301/311
Coleman et al, ⁵⁶ New Zealand	22-24	116 (26.7)	Women with essential or secondary hypertension, renal disease, systemic lupus erythematosus, antiphospholipid syndrome, previous pre-eclampsia or placental abruption. Excluded: Women with multiple pregnancy, fetal abnormalities	<p>Blood pressure \geq 140/90 mm Hg with rise in diastolic blood pressure > 15 mm Hg twice, 4 h apart; proteinuria \geq 0.3 g protein in 24-h urine collection or dipstick 2+</p> <p>Superimposed pre-eclampsia: Blood pressure > 140/90 mm Hg with rise in systolic blood pressure \geq 30 or diastolic blood pressure \geq 15 mm Hg with new proteinuria or doubling of existing proteinuria</p>	Transabdominal, colour, crossover	<ul style="list-style-type: none"> Any resistance index > 0.58 Both resistance indexes > 0.58 Any resistance index \geq 0.7 Both resistance indices \geq 0.7 Any notching Bilateral notching Resistance index > 0.58 and any notching Resistance index \geq 0.7 and any notching Both resistance indices \geq 0.7 and any notching 	<ul style="list-style-type: none"> 29/31 13/31 16/31 7/31 20/31 9/31 20/31 13/31 6/31 	<ul style="list-style-type: none"> 36/84 65/84 60/84 79/84 60/84 72/84 60/84 66/84 79/84
Driul et al, ⁵⁷ Italy	20	103 (37.9)	Women with chronic hypertension, diabetes mellitus, previous fetal death, intrauterine growth restriction, multiple pregnancy, hydrops fetalis, previous pre-eclampsia, vascular and connective tissue disease, nephropathy, antiphospholipid syndrome, obesity, African-Italian race. All negative for lupus anticoagulant and anticardiolipin antibodies, all used folic acid, no family or personal history of thromboembolic disease (case-control)	American College of Obstetricians and Gynecologists criteria ⁷⁷	Unreported route, colour + pulsed wave, crossover	Resistance index > 0.58 and bilateral notching	23/39	60/64

continued

Appendix 3B: Patients at high risk for pre-eclampsia (part 3 of 6)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Ferrier et al, ⁵⁸ Australia	19-24	51 (7.8)	Women with renal disease other than diabetic nephropathy	Blood pressure \geq 140/90 mm Hg and rise in diastolic blood pressure \geq 15 mm Hg twice, 4 h apart; proteinuria > 0.3 g protein in 24-h urine collection or doubling of protein excretion in 24-h urinary collection if proteinuria already present < 20 wk	Transabdominal, colour, crossover	<ul style="list-style-type: none"> Resistance index > 90th centile A/C ratio > 90th centile 	<ul style="list-style-type: none"> 2/4 2/4 	<ul style="list-style-type: none"> 35/47 37/47
Frusca et al, ⁵⁹ Italy	24-25	78 (3.9)	Women with chronic hypertension. Excluded: women with multiple pregnancy, fetal anomalies	Superimposed pre-eclampsia: aggravated hypertension (rise in diastolic blood pressure > 15 mm Hg) and proteinuria > 0.3 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> Resistance index > 2 SD Any notching Bilateral notching 	<ul style="list-style-type: none"> 3/3 3/3 3/3 	<ul style="list-style-type: none"> 53/75 50/75 65/75
Frusca et al, ⁶⁰ Italy	24	56 (5.4)	Women with previous history of pre-eclampsia and who had normal blood pressure after that pregnancy	Diastolic blood pressure \geq 90 mm Hg twice, 4 h apart, in third trimester, proteinuria > 0.3 g protein in 24-h urine collection, no urinary tract infection	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> Resistance index > 0.58 Any notching Bilateral notching and mean resistance index > 0.58 	<ul style="list-style-type: none"> 3/3 3/3 1/3 	<ul style="list-style-type: none"> 32/53 35/53 46/53
Geipel et al, ⁶¹ Germany	18-24	256 (8.6)	Women with dichorionic twins. Excluded: women with fetal malformation, preterm prelabour rupture of membranes, unclear chorionicity, unavailable outcome	Blood pressure \geq 140/90 mm Hg repeated, proteinuria \geq 0.3 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> Unilateral or bilateral notching: twin reference Resistance index > 95th centile: singleton reference Resistance index > 95th centile: twin reference Resistance index > 95th and notching: twin reference Bilateral notching only 	<ul style="list-style-type: none"> 9/22 4/22 8/22 7/22 4/22 	<ul style="list-style-type: none"> 201/234 230/234 206/234 217/234 224/234
Geipel et al, ¹⁷ Germany	18-24	114 (5.3)	Patients who underwent intracytoplasmic sperm injection, women with singleton pregnancy	Blood pressure \geq 140/90 mm Hg repeated, proteinuria \geq 0.5 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Bilateral notching	6/6	87/108
Geipel et al, ¹⁷ Germany	18-24	32 (3.2)	Patients who underwent intracytoplasmic sperm injection, women with twin pregnancy	Blood pressure \geq 140/90 mm Hg repeated, proteinuria \geq 0.5 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Bilateral notching + mean resistance index > 0.55 or unilateral notching + mean resistance index > 0.65 or no notching + resistance index > 0.70	0/1	23/31

continued

Appendix 3B: Patients at high risk for pre-eclampsia (part 4 of 6)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Geipel et al, ¹⁷ Germany	18-24	32 (6.3)	Women with twin pregnancy (control group for patients who underwent intracytoplasmic sperm injection)	Blood pressure \geq 140/90 mm Hg repeated, proteinuria \geq 0.5 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Bilateral notching + mean resistance index $>$ 0.55 or unilateral notching + mean resistance index $>$ 0.65 or no notching + resistance index $>$ 0.70 (low risk)	2/2	24/30
Haddad et al, ⁶² France	23.8 \pm 2.6	48 (10.4)	Women given ASA therapy because of poor previous outcome, pre-eclampsia, eclampsia, HELLP syndrome, abruption, intrauterine growth restriction, intrauterine stillbirth	Systolic blood pressure \geq 140 or diastolic blood pressure \geq 90 mm Hg, proteinuria \geq 0.5 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	D/S ratio $<$ 10th centile or unilateral notching	5/5	22/43
Harrington et al, ²⁰ United Kingdom	19-21	170 (28.8)	Women with chronic hypertension, previous pre-eclampsia, gestational hypertension, intrauterine growth restriction, preterm labour, abruption, intrauterine stillbirth, diabetes mellitus, renal disease, other medical diseases. Excluded: women with fetal anomalies	Diastolic blood pressure \geq 90 mm Hg twice, 4 h apart, or \geq 110 mm Hg once; proteinuria $>$ 0.3 g in 24-h urine collection or dipstick 2+ twice, 4 h apart; no urinary tract infection	Unreported route, colour + pulsed wave, crossover	Bilateral notching + mean resistance index \geq 0.55 (50th centile) or unilateral notching + mean resistance index \geq 0.65 (80th centile)	19/20	120/150
Hershkovitz et al, ⁶³ United Kingdom	20-24	88 (44.3)	Women with chronic hypertension, history of severe pre-eclampsia, thrombophilia	Blood pressure \geq 140/90 mm Hg twice, 4 h apart, $>$ 20 wk, rise in diastolic blood pressure \geq 20 mm Hg, proteinuria \geq 0.3 g protein in 24-h urine collection or dipstick 2+	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> Bilateral abnormal Doppler (PI $>$ 95th centile or notching) Any abnormal Doppler (PI $>$ 95th centile or notching) 	<ul style="list-style-type: none"> • 12/39 • 21/39 	<ul style="list-style-type: none"> • 39/49 • 37/49
Konchak et al, ⁶⁴ United States	17-22	103 (5.8)	Women with α -fetoprotein $>$ 2.0 multiples of the median twice or $>$ 2.5 multiples of the median once. Women with singleton pregnancy, no fetal anomalies, normal amniotic fluid volume	Not specified	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> Unilateral notching Resistance index $>$ 95th centile 	<ul style="list-style-type: none"> • 5/6 • 5/6 	<ul style="list-style-type: none"> • 93/97 • 91/97
Le Thi Huong et al, ⁶⁵ France	2nd trimester	100 (7.0)	Women with systemic lupus erythematosus, antiphospholipid syndrome	Diastolic blood pressure $>$ 90 mm Hg, proteinuria \geq 0.5 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Any notching	5/7	80/93

continued

Appendix 3B: Patients at high risk for pre-eclampsia (part 5 of 6)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Nagtegaal et al, ⁶⁶ Australia	18-22	182 (24.7)	Women with previous pre-eclampsia, intrauterine growth restriction, placental abruption, recurrent miscarriages, unexplained stillbirth, chronic hypertension, type 1 diabetes mellitus, thrombophilia, family history of pre-eclampsia	According to ASSHP criteria ⁷⁸	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Resistance index ≥ 0.58 • Resistance index ≥ 0.58 + any notching • Resistance index ≥ 0.58 + bilateral notching • Resistance index ≥ 0.65 • Resistance index ≥ 0.65 + any notching • Resistance index ≥ 0.65 + bilateral notching 	<ul style="list-style-type: none"> • 31/45 • 7/45 • 2/45 • 26/45 • 6/45 • 2/45 	<ul style="list-style-type: none"> • 43/137 • 104/137 • 125/137 • 57/137 • 104/137 • 125/137
Parretti et al, ⁶⁷ Italy	24	144 (25.0)	Normotensive, white women with risk factors (previous pre-eclampsia, stillbirth, placental abruption, intrauterine growth restriction). Excluded: smokers, women with cardiovascular or renal disease, diabetes mellitus, multiple pregnancy, and fetal chromosomal abnormalities, and women receiving low-dose ASA therapy	Blood pressure > 140/90 mm Hg twice within 24 h, proteinuria > 0.3 g protein in 24-h urine collection, no urinary tract infection, previously normotensive and nonproteinuric	Unreported route, colour + pulsed wave, crossover	Mean resistance index ≥ 0.58	28/36	73/108
Pattinson et al, ⁶⁸ South Africa	16-28	53 (13.2)	Women at high risk of complications	Davey and MacGillivray criteria ⁷⁶	Unreported route, colour + pulsed wave, crossover	Resistance index > 0.58	6/7	32/46
Rizzo et al, ⁶⁹ Italy	20-24	64 (25.0)	Women with twin pregnancy, certain gestational age (first trimester crown-rump length or second trimester biparietal diameter), successful Doppler ultrasonography of both uterine arteries, dichorionicity (prenatally and postnatally confirmed)	Diastolic blood pressure ≥ 90 mm Hg twice, 4 h apart, in previously normotensive and nonproteinuric or diastolic blood pressure ≥ 110 mm Hg once, proteinuria ≥ 0.3 g protein in 24-h urine collection (Davey and MacGillivray criteria ⁷⁶)	Unreported route, colour + pulsed wave, crossover	Mean resistance index (no cutoff)	6/16	32/48

continued

Appendix 3B: Patients at high risk for pre-eclampsia (part 6 of 6)

Study, country	Gestation, wk	Total no. of patients (% with pre-eclampsia)	Patient group (study design*)	Reference standard for pre-eclampsia	Details of index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Soregaroli et al, ⁷⁰ Italy	24	271 (3.3)	Women with high-risk pregnancy (history of gestational hypertension, pre-eclampsia, intrauterine growth restriction, intrauterine demise, chronic hypertension, autoimmune disease, renal disease). Excluded: Women with multiple pregnancy, fetal chromosomal anomalies, pregnancy complications < 24 wk	Blood pressure > 140/90 mm Hg twice, 4 h apart, > 20 wks; proteinuria > 0.3 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	Resistance index > 0.6	9/9	186/262
Vainio et al, ⁴⁵ Finland	12-14	72 (15.3)	Women at high risk of pre-eclampsia. Excluded: those with gestation < 12 or > 14 wk, asthma, allergy to ASA, peptic ulcer, prostaglandin inhibitors < 10 d of investigation	Blood pressure ≥ 140/90 mm Hg, proteinuria ≥ 0.3 g protein in 24-h urine collection or dipstick 1+	Unreported route, colour + pulsed wave, crossover	Bilateral notching	10/11	28/61
Valensise et al, ⁷¹ Italy	22 and 24	16 (43.8)	Women with chronic hypertension	Davey and MacGillivray criteria ⁷⁶ for superimposed pre-eclampsia, not quantified	Unreported route, colour + pulsed wave, crossover	Resistance index > 0.58 or notching	6/7	7/9
Venkat-raman et al, ⁷² United Kingdom	16-18 22-24	164 (9.8)	Women who had had recurrent miscarriage and are positive for antiphospholipid antibodies (no systemic lupus erythematosus or thromboembolic disease)	Blood pressure ≥ 140/90 mm Hg twice, 4 h apart, or diastolic blood pressure ≥ 110 mm Hg once, proteinuria ≥ 0.3 g protein in 24-h urine collection	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Any notching • Bilateral notching • Any notching • Bilateral notching 	<ul style="list-style-type: none"> • 10/16 • 6/16 • 6/16 • 4/16 	<ul style="list-style-type: none"> • 81/148 • 121/148 • 126/148 • 139/148
Yu et al, ⁷³ United Kingdom	22-24	351 (6.0)	Women with twin pregnancy, 2 live fetuses, no fetal abnormality, no twin transfusion syndrome	Diastolic blood pressure ≥ 90 mm Hg twice, 4 h apart, in previously normotensive women, proteinuria ≥ 0.3 g protein in 24-h urine collection or dipstick ≥ 2+ twice with midstream urine if no 24-h collection available (International Society for the Study of Hypertension in Pregnancy criteria ⁷⁵)	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Pulsatility index > 95th centile • Bilateral notching only • Pulsatility index > 95th centile and bilateral notching 	<ul style="list-style-type: none"> • 7/21 • 4/21 • 4/21 	<ul style="list-style-type: none"> • 319/330 • 322/330 • 327/330
Zeeman et al, ⁷⁴ United States	16-20	52 (21.2)	Women with chronic hypertension requiring medication	Blood pressure exceeding early pregnancy values, proteinuria ≥ 0.3 g protein in 24-h urine collection or dipstick ≥ 1+ (30 mg/dL)	Unreported route, colour + pulsed wave, crossover	Pulsatility index > 95th centile	4/11	29/41

Note: A/C ratio = ratio of peak systolic to early diastolic velocity; ASA = acetylsalicylic acid; D/S ratio = ratio of diastolic to systolic velocity; FN = false negative; FP = false positive; HELLP syndrome = hemolytic anemia, elevated liver enzyme levels, low platelet count; S/D ratio = ratio of peak systolic to late diastolic velocity; SD = standard deviation; TN = true negative; TP = true positive.

*Cohort study unless stated otherwise.

See next page for references.

Appendix to Crossen JS, Morris RK, ter Riet G, et al. Uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariate meta-analysis. *CMAJ* 2008;178(6):701-11

References

1. Aardema MW, De Wolf BT, Saro MC, et al. Quantification of the diastolic notch in Doppler ultrasound screening of uterine arteries. *Ultrasound Obstet Gynecol* 2000;16:630-4.
2. Albaiges G, Missfelder-Lobos H, Lees C, et al. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol* 2000;96:559-64.
3. Antsaklis A, Daskalakis G, Tzortzis E, et al. The effect of gestational age and placental location on the prediction of pre-eclampsia by uterine artery Doppler velocimetry in low-risk nulliparous women. *Ultrasound Obstet Gynecol* 2000;16:635-9.
4. Aquilina J, Thompson O, Thilaganathan B, et al. Improved early prediction of pre-eclampsia by combining second-trimester maternal serum inhibin-A and uterine artery Doppler. *Ultrasound Obstet Gynecol* 2001;17:477-84.
5. Aquilina J, Barnett A, Thompson O, et al. Comprehensive analysis of uterine artery flow velocity waveforms for the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2000;16:163-70.
6. Arenas J, Fernandez I, Rodriguez-Mon C, et al. Doppler screening of the uterine arteries to predict complications during pregnancy [in Spanish]. *Clinica e Investigacion en Ginecologia y Obstetricia* 2003;30:178-84.
7. Audibert F, Benchimol Y, Benattar C, et al. Prediction of preeclampsia or intrauterine growth restriction by second trimester serum screening and uterine Doppler velocimetry. *Fetal Diagn Ther* 2005;20:48-53.
8. Ay E, Kavak ZN, Elter K, et al. Screening for pre-eclampsia by using maternal serum inhibin A, activin A, human chorionic gonadotropin, unconjugated estriol, and alpha-fetoprotein levels and uterine artery Doppler in the second trimester of pregnancy. *Aust N Z J Obstet Gynaecol* 2005;45:283-8.
9. Bassim S, Lange M, Salzer H. Uterine artery doppler and pregnancy complications in unselected women [in German]. *Geburtshilfe und Frauenheilkunde* 2006;66:59-62.
10. Bower S, Schuchter K, Campbell S. Doppler ultrasound screening as part of routine antenatal scanning: prediction of pre-eclampsia and intrauterine growth retardation. *BJOG* 1993;100:989-94.
11. Bower S, Bewley S, Campbell S. Improved prediction of preeclampsia by two-stage screening of uterine arteries using the early diastolic notch and color Doppler imaging. *Obstet Gynecol* 1993;82:78-83.
12. Caforio L, Testa AC, Mastromarino C, et al. Predictive value of uterine artery velocimetry at midgestation in low- and high-risk populations: a new perspective. *Fetal Diagn Ther* 1999;14:201-5.
13. Campbell S, Black RS, Lees CC, et al. Doppler ultrasound of the maternal uterine arteries: disappearance of abnormal waveforms and relation to birthweight and pregnancy outcome. *Acta Obstet Gynecol Scand* 2000;79:631-4.
14. Carbillon L, Uzan M, Largilliere C, et al. Prospective evaluation of uterine artery flow velocity waveforms at 12-14 and 22-24 weeks of gestation in relation to pregnancy outcome and birth weight. *Fetal Diagn Ther* 2004;19:381-4.
15. Driul L, Springolo F, Pezzani I, et al. Pathological monolateral Doppler velocimetry of the uterine artery and materno-fetal outcome [Italian]. *Minerva Ginecol* 2002;54:397-402.
16. Frusca T, Soregaroli M, Valcamonica A, et al. Doppler velocimetry of the uterine arteries in nulliparous women. *Early Hum Dev* 1997;48:177-85.
17. Geipel A, Ludwig M, Germer U, et al. Uterine artery Doppler velocimetry and the outcome of pregnancies resulting from ICSI. *Hum Reprod* 2001;16:1397-402.
18. Gómez O, Martínez JM, Figueras F, et al. Uterine artery Doppler at 11-14 weeks of gestation to screen for hypertensive disorders and associated complications in an unselected population. *Ultrasound Obstet Gynecol* 2005;26:490-4.
19. Hafner E, Metzzenbauer M, Hofinger D, et al. Comparison between three-dimensional placental volume at 12 weeks and uterine artery impedance/notching at 22 weeks in screening for pregnancy-induced hypertension, pre-eclampsia and fetal growth restriction in a low-risk population. *Ultrasound Obstet Gynecol* 2006;27:652-7.
20. Harrington K, Fayyad A, Thakur V, et al. The value of uterine artery Doppler in the prediction of uteroplacental complications in multiparous women. *Ultrasound Obstet Gynecol* 2004;23:50-5.
21. Harrington K, Carpenter RG, Goldfrad C, et al. Transvaginal Doppler ultrasound of the uteroplacental circulation in the early prediction of pre-eclampsia and intrauterine growth retardation. *BJOG* 1997;104:674-81.
22. Harrington K, Cooper D, Lees C, et al. Doppler ultrasound of the uterine arteries: the importance of bilateral notching in the prediction of pre-eclampsia, placental abruption or delivery of a small-for-gestational-age baby. *Ultrasound Obstet Gynecol* 1996;7:182-8.
23. Harrington KF, Campbell S, Bewley S, et al. Doppler velocimetry studies of the uterine artery in the early prediction of pre-eclampsia and intra-uterine growth retardation. *Eur J Obstet Gynecol Reprod Biol* 1991;42(Suppl):S14-S20.
24. Kurdi W, Campbell S, Aquilina J, et al. The role of color Doppler imaging of the uterine arteries at 20 weeks' gestation in stratifying antenatal care. *Ultrasound Obstet Gynecol* 1998;12:339-45.
25. Madazli R, Kuseyrioglu B, Uzun H, et al. Prediction of preeclampsia with maternal mid-trimester placental growth factor, activin A, fibronectin and uterine artery Doppler velocimetry. *Int J Gynaecol Obstet* 2005;89:251-7.
26. Marchesoni D, Pezzani I, Springolo F, et al. The use of uterine artery Doppler as a screening test for pre-eclampsia. *Ital J Gynaecol Obstet* 2003;15:15-20.
27. Martin AM, Bindra R, Curcio P, et al. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11-14 weeks of gestation. *Ultrasound Obstet Gynecol* 2001;18:583-6.
28. Mires GJ, Williams FL, Leslie J, et al. Assessment of uterine arterial notching as a screening test for adverse pregnancy outcome. *Am J Obstet Gynecol* 1998;179:1317-23.
29. Morris JM, Fay RA, Ellwood DA, et al. A randomized controlled trial of aspirin in patients with abnormal uterine artery blood flow. *Obstet Gynecol* 1996;87:74-8.
30. Nicolaides KH, Bindra R, Turan OM, et al. A novel approach to first-trimester screening for early pre-eclampsia combining serum PP-13 and Doppler ultrasound. *Ultrasound Obstet Gynecol* 2006;27:13-7.
31. North RA, Ferrier C, Long D, et al. Uterine artery Doppler flow velocity waveforms in the second trimester for the prediction of preeclampsia and fetal growth retardation. *Obstet Gynecol* 1994;83:378-6.

32. Ohkuchi A, Minakami H, Sato I, et al. Predicting the risk of pre-eclampsia and a small-for-gestational-age infant by quantitative assessment of the diastolic notch in uterine artery flow velocity waveforms in unselected women. *Ultrasound Obstet Gynecol* 2000;16:171-8.
33. Onalan R, Onalan G, Gunenc Z, et al. Combining 2nd-trimester maternal serum homocysteine levels and uterine artery Doppler for prediction of preeclampsia and isolated intrauterine growth restriction. *Gynecol Obstet Invest* 2005;61:142-8.
34. Papageorgiou AT, Yu CK, Erasmus IE, et al. Assessment of risk for the development of pre-eclampsia by maternal characteristics and uterine artery Doppler. *BJOG* 2005;112:703-9.
35. Park YW, Lim JC, Kim YH, et al. Uterine artery Doppler velocimetry during mid-second trimester to predict complications of pregnancy based on unilateral or bilateral abnormalities. *Yonsei Med J* 2005;46:652-7.
36. Parra M, Rodrigo R, Barja P, et al. Screening test for preeclampsia through assessment of uteroplacental blood flow and biochemical markers of oxidative stress and endothelial dysfunction. *Am J Obstet Gynecol* 2005;193:1486-91.
37. Phupong V, Dejthevaporn T, Tanawattanacharoen S, et al. Predicting the risk of preeclampsia and small for gestational age infants by uterine artery Doppler in low-risk women. *Arch Gynecol Obstet* 2003;268:158-61.
38. Prefumo F, Bhide A, Sairam S, et al. Effect of parity on second-trimester uterine artery Doppler flow velocity and waveforms. *Ultrasound Obstet Gynecol* 2004;23:46-9.
39. Sato H. A study for predicting toxemia of pregnancy by the diastolic notch in pulsed Doppler flow velocity waveforms of the uterine arteries – quantitative analysis of the diastolic notch as uterine arterial index (UTAI) [in Japanese]. *Nippon Sanka Fujinka Gakkai Zasshi* 1995;47:1055-62.
40. Schwarze A, Nelles I, Krapp M, et al. Doppler ultrasound of the uterine artery in the prediction of severe complications during low-risk pregnancies. *Arch Gynecol Obstet* 2005;271:46-52.
41. Soutif C, Prevost A, André M. Value of the systematic uterine Doppler in the primiparous woman. a series of 315 cases [in French]. *J Gynecol Obstet Biol Reprod (Paris)* 1996;25:819-23.
42. Subtil D, Goeusse P, Houfflin-Debauge V, et al. Randomised comparison of uterine artery Doppler and aspirin (100 mg) with placebo in nulliparous women: the Essai Regional Aspirine Mère-Enfant study (part 2). *BJOG* 2003;110:485-91.
43. Tranquilli AL, Giannubilo SR, Bezzeccheri V, et al. The relative weight of Doppler of the uterine artery and 24-h ambulatory blood pressure monitoring in predicting hypertension in pregnancy and preeclampsia [in Italian]. *Acta Biomed Ateneo Parmense* 2000;71(Suppl 1):351-5.
44. Uludag S, Madazli R, Benian A, et al. The relationship between maternal serum alfa fetoprotein and uterine artery Doppler findings at 20-24 weeks' gestation for prediction of preeclampsia and intrauterine growth retardation. *Marmara Med J* 2002;15:169-74.
45. Vainio M, Kujansuu E, Koivisto AM, et al. Bilateral notching of uterine arteries at 12-14 weeks of gestation for prediction of hypertensive disorders of pregnancy. *Acta Obstet Gynecol Scand* 2005;84:1062-7.
46. Valensise H, Romanini C. Second-trimester uterine artery flow velocity waveform and oral glucose tolerance test as a means of predicting intrauterine growth retardation. *Ultrasound Obstet Gynecol* 1993;3:412-6.
47. Valensise H, Bezzeccheri V, Rizzo G, et al. Doppler velocimetry of the uterine artery as a screening test for gestational hypertension. *Ultrasound Obstet Gynecol* 1993;3:18-22.
48. Yu CK, Smith GC, Papageorgiou AT, et al. An integrated model for the prediction of pre-eclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women. *Am J Obstet Gynecol* 2005;193:429-36.
49. Zimmermann P, Eirio V, Koskinen J, et al. Effect of low-dose aspirin treatment on vascular resistance in the uterine, uteroplacental, renal and umbilical arteries: a prospective longitudinal study on a high risk population with persistent notch in the uterine arteries. *Eur J Ultrasound* 1997;5:17-30.
50. Aardema MW, Lander M, Oosterhof H, et al. Doppler ultrasound screening predicts recurrence of poor pregnancy outcome in subsequent pregnancies, but not the recurrence of PIH or preeclampsia. *Hypertens Pregnancy* 2000;19:281-8.
51. Alkazaleh F, Chaddha V, Viero S, et al. Second-trimester prediction of severe placental complications in women with combined elevations in alpha-fetoprotein and human chorionic gonadotrophin. *Am J Obstet Gynecol* 2006;194:821-7.
52. Axt-Fliedner R, Schwarze A, Nelles I, et al. The value of uterine artery Doppler ultrasound in the prediction of severe complications in a risk population. *Arch Gynecol Obstet* 2005;271:53-8.
53. Caruso A, Caforio L, Testa AC, et al. Chronic hypertension in pregnancy: color Doppler investigation of uterine arteries as a predictive test for superimposed preeclampsia and adverse perinatal outcome. *J Perinat Med* 1996;24:141-53.
54. Caruso A, De Carolis S, Ferrazzani S, et al. Pregnancy outcome in relation to uterine artery flow velocity waveforms and clinical characteristics in women with antiphospholipid syndrome. *Obstet Gynecol* 1993;82:970-7.
55. Chan FY, Pun TC, Lam C, et al. Pregnancy screening by uterine artery Doppler velocimetry: Which criterion performs best? *Obstet Gynecol* 1995;85:596-602.
56. Coleman MA, McCowan LM, North RA. Mid-trimester uterine artery Doppler screening as a predictor of adverse pregnancy outcome in high-risk women. *Ultrasound Obstet Gynecol* 2000;15:7-12.
57. Driul L, Damante G, D'Elia A, et al. Genetic thrombophilias and uterine artery Doppler velocimetry and preeclampsia. *Int J Gynaecol Obstet* 2005;88:265-70.
58. Ferrier C, North RA, Becker G, et al. Uterine artery waveform as a predictor of pregnancy outcome in women with underlying renal disease. *Clin Nephrol* 1994;42:362-8.
59. Frusca T, Soregaroli M, Zanelli S, et al. Role of uterine artery Doppler investigation in pregnant women with chronic hypertension. *Eur J Obstet Gynecol Reprod Biol* 1998;79:47-50.
60. Frusca T, Soregaroli M, Danti L, et al. Uterine artery velocimetry as a screening test in patients with previous preeclampsia. *Ital J Gynaecol Obstet* 1996;8:94-8.
61. Geipel A, Berg C, Germer U, et al. Doppler assessment of the uterine circulation in the second trimester in twin pregnancies: prediction of pre-eclampsia, fetal growth restriction and birth weight discordance. *Ultrasound Obstet Gynecol* 2002;20:541-5.

62. Haddad B, Uzan M, Bréart G, et al. Uterine Doppler wave form and the prediction of the recurrence of pre-eclampsia and intra-uterine growth retardation in patients treated with low-dose aspirin. *Eur J Obstet Gynecol Reprod Biol* 1995;62:179-83.
63. Hershkovitz R, de Swiet M, Kingdom J. Mid-trimester placentation assessment in high-risk pregnancies using maternal serum screening and uterine artery Doppler. *Hypertens Pregnancy* 2005;24:273-80.
64. Konchak PS, Bernstein IM, Capeless EL. Uterine artery Doppler velocimetry in the detection of adverse obstetric outcomes in women with unexplained elevated maternal serum alpha-fetoprotein levels. *Am J Obstet Gynecol* 1995;173:1115-9.
65. Le Thi Huong D, Wechsler B, Vauthier-Brouzes D, et al. The second trimester Doppler ultrasound examination is the best predictor of late pregnancy outcome in systemic lupus erythematosus and/or the antiphospholipid syndrome. *Rheumatology (Oxford)* 2006;45:332-8.
66. Nagtegaal MJ, van Rijswijk S, McGavin S, et al. Use of uterine Doppler in an Australian level II maternity hospital. *Aust N Z J Obstet Gynaecol* 2005;45:424-9.
67. Parretti E, Mealli F, Magrini A, et al. Cross-sectional and longitudinal evaluation of uterine artery Doppler velocimetry for the prediction of pre-eclampsia in normotensive women with specific risk factors. *Ultrasound Obstet Gynecol* 2003;22:160-5.
68. Pattinson RC, Brink AL, De Wet PE, et al. Early detection of poor fetal prognosis by serial Doppler velocimetry in high-risk pregnancies. *S Afr Med J* 1991;80:428-31.
69. Rizzo G, Arduini D, Romanini C. Uterine artery Doppler velocity waveforms in twin pregnancies. *Obstet Gynecol* 1993;82:978-83.
70. Soregaroli M, Valcamonica A, Scalvi L, et al. Late normalisation of uterine artery velocimetry in high risk pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2001;95:42-5.
71. Valensise H, Romanini C. Uterine Doppler in the identification of patients at risk for hypertension and IUGR. *J Perinat Med* 1994;22 Suppl 1:69-72.
72. Venkat-Raman N, Backos M, Teoh TG, et al. Uterine artery Doppler in predicting pregnancy outcome in women with antiphospholipid syndrome. *Obstet Gynecol* 2001;98:235-42.
73. Yu CK, Papageorghiou AT, Boli A, et al. Screening for pre-eclampsia and fetal growth restriction in twin pregnancies at 23 weeks of gestation by transvaginal uterine artery Doppler. *Ultrasound Obstet Gynecol* 2002;20:535-40.
74. Zeeman GG, McIntire DD, Twickler DM. Maternal and fetal artery Doppler findings in women with chronic hypertension who subsequently develop superimposed pre-eclampsia. *J Matern Fetal Neonatal Med* 2003;14:318-23.
75. Brown MA, Lindheimer MD, de Swiet M, et al. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001;20:IX-XIV.
76. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 1988;158:892-8.
77. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. ACOG Technical Bulletin, vol 219. Washington (DC): The College; 1996.
78. Brown MA, Hague WM, Higgins J, et al. The detection, investigation and management of hypertension in pregnancy. *Aust N Z Obstet Gynecol* 2000;40:133-55.