

Appendix 4: Characteristics of studies of uterine artery Doppler ultrasonography used to predict intrauterine growth restriction in patients at low risk or unspecified risk (Appendix 4A) and in patients at high risk (Appendix 4B)

Appendix 4A: Patients at low risk or unspecified risk of intrauterine growth restriction (part 1 of 6)

Study, country	Gestation, wk	Total no. of patients (% with intrauterine growth restriction)	Patient group (study design*)	Reference standard for intrauterine growth restriction	Details of index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Albaiges et al, ¹ United Kingdom	22-25	1757 (8.9 for birth weight < 10th centile; 2.9 for birth weight < 3rd centile)	Women with singleton pregnancy receiving routine antenatal care	a) Birth weight < 10th centile b) Birth weight < 3rd centile (local and gestational values)	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Bilateral notching or mean pulsatility index > 1.45 (95th centile) • Bilateral notching only • Mean pulsatility index > 1.45 only • Mean pulsatility index > 1.45 + bilateral notching 	a) 32/143 b) 16/52 a) 19/143 b) 12/52 a) 30/143 b) 35/52 a) 17/143 b) 12/40	a) 1518/1614 b) 1593/1705 a) 1556/1614 b) 1637/1705 a) 1554/1614 b) 1621/1705 a) 1593/1614 b) 1678/1705
Arenas et al, ² Spain	20	319 (8.2)	Women at unspecified risk. Excluded: women with multiple pregnancy, congenital defects	Birth weight < 10th centile (local and gestational values)	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Mean resistance index ≥ 0.59 (75th centile) • Mean resistance index ≥ 0.52 (50th centile) • Mean resistance index ≥ 0.65 (90th centile) • Mean resistance index ≥ 0.71 (95th centile) 	<ul style="list-style-type: none"> • 12/26 • 16/26 • 5/26 • 3/26 	<ul style="list-style-type: none"> • 216/293 • 134/293 • 261/293 • 277/293
Audibert et al, ³ France	18-26	2615 (8.8)	Women who had α-fetoprotein and human chorionic gonadotrophin 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 at 18-26 wk, delivery < 24 wk	Birth weight < 10th centile (local values)	Unreported route, type and site	<ul style="list-style-type: none"> • Bilateral notching • Unilateral notching 	<ul style="list-style-type: none"> • 30/230 • 52/230 	<ul style="list-style-type: none"> • 2300/2385 • 2118/2385
Bassim et al, ⁴ Switzerland	20-24	490 (5.3)	Women who underwent routine screening	Birth weight < 10th (local values)	Transabdominal, unreported type, crossover	Bilateral notching	8/26	436/464
Bower et al, ⁵ United Kingdom	18-22	2058 (10.9, 5.2 and 3.5 for birth weight < 10th, 5th and 3rd centiles, respectively)	Women at unspecified risk. Excluded: women with multiple pregnancy, gestational age outside study limits, fetal anomalies	<ul style="list-style-type: none"> • Birth weight < 10th centile • Birth weight < 5th centile • Birth weight < 3rd centile (local and gestational values) 	Transabdominal, continuous wave, crossover	<ul style="list-style-type: none"> • Resistance index > 95th centile either side or any notching • Birth weight < 10th centile • Birth weight < 5th centile • Birth weight < 3rd centile 	<ul style="list-style-type: none"> • 84/225 • 49/106 • 34/73 	<ul style="list-style-type: none"> • 1588/1833 • 1672/1833 • 1690/1833

continued

Appendix 4A: Patients at low risk or unspecified risk of intrauterine growth restriction (part 2 of 6)

Study, country	Gestation, wk	Total no. of patients (% with intrauterine growth restriction)	Patient group (study design*)	Reference standard for intrauterine growth restriction	Details of index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Caforio et al, ⁶ Italy	18-20 22-24	530 (5.1) 530 (10.9)	Healthy nulliparous women. Excluded: women with congenital defects, chromosomal abnormalities, multiple pregnancies, infections, Rhesus isoimmunization, non-immune hydrops, preterm prelabour rupture of membranes, intrauterine demise, delivery < 26 weeks	a) Birth weight < 1750 g b) Birth weight < 2500 g	Unreported route, colour + pulsed wave, crossover	Resistance index > 90th centile • Gestational age 18-20 wk • Gestational age 22-24 wk	a) 16/27 b) 33/58 a) 14/27 b) 31/63	a) 355/502 b) 338/472 a) 378/505 b) 369/467
Carbillon et al, ⁷ France	12-14 22-24	243 (9.4)	Women undergoing routine ultrasound screening	Fetal growth restriction no threshold	Transabdominal, unreported type, ascending branch	• No notching at 12-14 wk v. unilateral or bilateral notching • Bilateral notching at 22-24 wk	• 19/23 • 6/23	• 100/220 • 205/220
Driul et al, ⁸ Italy	24	830 (1.8)	Not reported	Fetal growth restriction unreported threshold	Unreported route, colour, crossover	Resistance index ≥ 0.6 or unilateral notching	8/15	722/825
Dugoff et al, ⁹ United Kingdom	10-14	1008 (1.2)	Women enrolled in FASTER trial. Excluded: women with structural or chromosomal anomalies, fetal genetic syndrome, intrauterine stillbirth < 24 wk, congenital uterine malformation	Birth weight < 10th centile (local and gestational values)	Transabdominal, colour + pulsed wave, crossover	• Mean resistance index ≥ 0.81 (95th) • Mean resistance index ≥ 0.78 (90th) • Mean resistance index ≥ 0.70 (75th)	• 2/12 • 4/12 • 8/12	• 947/996 • 894/996 • 748/996
Frusca et al, ¹⁰ Italy	24	419 (7.1) 419 (2.6)	Nulliparous women without risk factors. Excluded: women with chronic hypertension, diabetes mellitus, autoimmune disease	• Birth weight < 10th centile (local and gestational values) • Birth weight < 3rd centile	Transabdominal, colour + pulsed wave, crossover	Resistance index > 0.58 • Birth weight < 10th centile • Birth weight < 3rd centile	• 13/30 • 6/11	• 366/389 • 378/408
Geipel et al, ¹¹ Germany	18-24	114 (8.8)	Women with singleton pregnancy (control group for women undergoing intracytoplasmic sperm injection)	Birth weight < 10th centile (local values)	Unreported route, colour, crossover	Bilateral notching + mean resistance index > 0.55 or unilateral notching + mean resistance index > 0.65 or no notching + mean resistance index > 0.7	5/10	85/104
Gomez et al, ¹² Spain	11-14	999 (3.7)	Women with singleton pregnancy attending for routine antenatal care. Excluded: Fetal anomalies, women treated with aspirin, heparin or antihypertensive medication before enrolment	Birth weight < 5th centile (local and gestational values)	Transvaginal, colour + pulsed wave, cervicocorporeal junction	Mean pulsatility index > 95th centile	9/37	918/962

continued

Appendix 4A: Patients at low risk or unspecified risk of intrauterine growth restriction (part 3 of 6)

Study, country	Gestation, wk	Total no. of patients (% with intrauterine growth restriction)	Patient group (study design*)	Reference standard for intrauterine growth restriction	Details of index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Hafner et al, ¹³ Germany	21-23	2489 (6.8)	All singleton pregnancies	Birth weight < 10th centile (unreported dataset)	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Bilateral notching • Mean pulsatility index \geq 90th 	<ul style="list-style-type: none"> • 37/168 • 34/168 	<ul style="list-style-type: none"> • 2132/2321 • 2103/2321
Harrington et al, ¹⁴ United Kingdom	12-16	623 (19.9)	Unselected singleton pregnancies	Birth weight < 10th centile (local and gestational values)	Transvaginal, unreported type and site	<ul style="list-style-type: none"> • Bilateral v. unilateral or no notching • Bilateral or unilateral v. no notching 	<ul style="list-style-type: none"> • 42/61 • 53/61 	<ul style="list-style-type: none"> • 399/562 • 268/562
Harrington et al, ¹⁵ United Kingdom	24	1204 (10.8)	Women at unspecified risk. Excluded: women with multiple pregnancy, fetal anomalies, pre-eclampsia or intrauterine growth restriction \leq 24 wk	Birth weight < 10th centile (local and gestational values)	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Any notching or mean resistance index > 95th centile • Unilateral or bilateral notching • Unilateral notching • Bilateral notching 	<ul style="list-style-type: none"> • 42/131 • 42/131 • 18/131 • 24/131 	<ul style="list-style-type: none"> • 1005/1073 • 1005/1073 • 1029/1073 • 1049/1073
Harrington et al, ¹⁶ United Kingdom	19-21	458 (5.2)	Multiparous women with singleton pregnancy at unspecified risk. Excluded: women with fetal anomalies	Birth weight < 5th centile (local values)	Transabdominal, colour + pulsed wave, crossover	Bilateral notching + mean resistance index \geq 0.55 (50th) or unilateral notching and mean resistance index \geq 0.65 (80th)	8/23	402/435
Jorn et al, ¹⁷ Germany	18-24	602 (4.8)	Not reported	Birth weight < 5th centile (local and gestational values)	Transabdominal, colour, ascending branch	Mean resistance index > 0.61	22/29	527/573
Kurdi et al, ¹⁸ United Kingdom	19-21	946 (16.5 and 6.0 for birth weight < 10th and 5th centiles, respectively)	Women at unspecified risk. Excluded: women with multiple pregnancy, fetal anomalies, or receiving low-dose ASA therapy	<ul style="list-style-type: none"> a) Birth weight < 10th centile b) Birth weight < 5th centile (local and gestational values) 	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Bilateral notching + mean resistance index > 0.55(50th) or unilateral notching + mean resistance index > 0.65 (90th), or no notching + mean resistance index > 0.70 (90th) • Bilateral notching + mean resistance index > 0.55 (50th) 	<ul style="list-style-type: none"> a) 70/156 b) 27/57 a) 70/156 b) 21/57 	<ul style="list-style-type: none"> a) 644/790 b) 700/889 a) 86/790 b) 793/889
Kurdi et al, ¹⁹ United Kingdom	19-21 and 24-26	779 (13.2 and 4.2 for birth weight < 10th and 3rd centiles, respectively)	Subgroup analysis of cohort in reference 18 with normalization of Doppler at 24-26 wk	<ul style="list-style-type: none"> a) Birth weight < 10th centile b) Birth weight < 3rd centile (local and gestational values) 	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Bilateral notching + mean resistance index > 0.55 (50th) or unilateral notching + mean resistance index > 0.65 (90th), or no notching + mean resistance index > 0.70 (90th) • Bilateral notching + mean resistance index > 0.55 (50th) 	<ul style="list-style-type: none"> a) 16/103 b) 29/33 a) 16/103 b) 29/33 	<ul style="list-style-type: none"> a) 643/676 b) 701/746 a) 643/676 b) 701/746
Liberati et al, ²⁰ Israel	22-24	481 (8.5)	Women with lateral placentas. Excluded: women with preterm delivery, multiple pregnancy, major fetal anomalies	Birth weight < 10th centile (local values)	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Mean resistance index \geq 90th centile • Unilateral notching or mean resistance index \geq 90th centile 	<ul style="list-style-type: none"> • 11/41 • 16/41 	<ul style="list-style-type: none"> • 422/440 • 406/440

continued

Appendix 4A: Patients at low risk or unspecified risk of intrauterine growth restriction (part 4 of 6)

Study, country	Gestation, wk	Total no. of patients (% with intrauterine growth restriction)	Patient group (study design*)	Reference standard for intrauterine growth restriction	Details of index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Marchesoni ²¹ (2003), Italy	24	900 (1.7)	Women at unspecified risk	Birth weight < 3rd centile	Unreported route and type, crossover	<ul style="list-style-type: none"> • Bilateral v. unilateral or no notching • Bilateral or uni v. no notching 	<ul style="list-style-type: none"> • 0/15 • 8/15 	<ul style="list-style-type: none"> • 825/885 • 722/885
Martin et al, ²² United Kingdom	11-14	3045 (9.5)	Routine antenatal care	Birth weight < 10th centile (local and gestational values)	Transabdominal, colour + pulsed wave, ascending branch	Mean pulsatility index > 2.35 (95th)	34/290	2639/2760
Miyakoshi et al, ²³ Japan	21-24	359 (11.4)	Not reported	Birth weight < 10th centile (local and gestational values)	Unreported route, colour + pulsed wave, crossover	Mean pulsatility index > 95th or unilateral notching	10/41	300/318
Morris et al, ²⁴ Australia	18	768 (12.7) 768 (4.6) 679 (10.9)	All nulliparous women (randomized controlled trial)	<ul style="list-style-type: none"> • Birth weight < 10th centile (local values) • Birth weight < 3rd centile • Pulsatility index < 10th centile 	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • S/D ratio > 3.0 (90th) + any notching or S/D ratio > 3.3 (2 SD) • Birth weight < 10th centile • Birth weight < 3rd centile • Pulsatility index < 10th centile 	<ul style="list-style-type: none"> • 21/98 • 9/35 • 15/74 	<ul style="list-style-type: none"> • 616/670 • 667/733 • 559/605
North et al, ²⁵ Australia	19-24	457 (6.6)	Healthy nulliparous women. Excluded: with renal disease, diabetes mellitus	Birth weight < 10th centile (local and gestational values)	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Resistance index > 90th centile • S/D 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"> • 15/30 • 14/30 • 17/30 • 16/30 • 16/30 • 16/30 • 14/30 	<ul style="list-style-type: none"> • 386/427 • 380/427 • 342/427 • 354/427 • 368/427 • 383/427 • 390/427
Ohkuchi et al, ²⁶ Japan	16-23	288 (6.3)	Women at unspecified risk with singleton pregnancy	Birth weight < 10th centile (local and gestational values)	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Resistance index > 70th centile • S/D ratio > 78th centile • Notch depth index > 0.14 • Any notching • Bilateral notching 	<ul style="list-style-type: none"> • 10/18 • 9/18 • 6/18 • 6/18 • 3/18 	<ul style="list-style-type: none"> • 168/270 • 201/270 • 249/270 • 217/270 • 225/270
Onalan et al, ²⁷ Turkey	19-21	406 (10.1)	Women whose fasting total serum homocysteine levels were measured. Excluded: women with multiple pregnancy, history of pre-eclampsia, hypertension < 20 wk, altered renal function, diabetes mellitus, chronic disease, fetal anomalies, folic acid use > 12 wk, special folate diet, treatment with antifolate drugs, age > 40 yr	Birth weight < 5th centile (local values)	Unreported route, type and site	Bilateral notching + mean resistance index > 0.55 or unilateral notching + mean resistance index > 0.65 or no notching + mean resistance index > 0.7	15/41	346/365
Papageorghiou et al, ²⁸ United Kingdom	20-24	7851 (9.4)	Women with singleton pregnancy attending for routine antenatal care	Birth weight < 10th centile (local and gestational values)	Transvaginal, colour + pulsed wave, level of internal cervical os	Mean pulsatility index > 1.63 (95th centile)	121/740	6831/7111

continued

Appendix 4A: Patients at low risk or unspecified risk of intrauterine growth restriction (part 5 of 6)

Study, country	Gestation, wk	Total no. of patients (% with intrauterine growth restriction)	Patient group (study design*)	Reference standard for intrauterine growth restriction	Details of index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Park et al, ²⁹ Korea	20-24	1090 (9.5)	Low-risk women. Excluded: women with multiple pregnancy, fetal anomalies, cardiovascular and renal diseases, diabetes mellitus, intrauterine growth restriction, pregnancy-induced hypertension, preterm labour before performance of Doppler	Birth weight < 10th centile (local and gestational values)	Transabdominal, colour + pulsed wave, previously reported	<ul style="list-style-type: none"> S/D ratio > 2 SD or any notching S/D ratio > 2 SD or bilateral notching only 	<ul style="list-style-type: none"> • 38/104 • 18/104 	<ul style="list-style-type: none"> • 759/986 • 935/986
Phupong et al, ³⁰ Thailand	22-28 (mean 24.9 [SD 1.9])	324 (1.9)	Healthy nulliparous and multiparous women. Excluded: women with multiple pregnancy, renal and cardiovascular disease, diabetes mellitus, fetal anomalies	Birth weight < 10th centile (gestational values)	Transabdominal, colour + pulsed wave, crossover	S/D ratio + 2 SD or bilateral notching	4/6	262/318
Prefumo et al, ³¹ United Kingdom	11-14 18-23	662 (9.8)	All singleton live births from clinical database. Excluded: multiparous women, women with fetal anomalies, concurrent maternal disease and gestational diabetes	Birth weight < 10th centile (local, gestational and sex values)	Unreported route, colour, ascending branch	Bilateral notching <ul style="list-style-type: none"> • Gestation 11-14 wk • Gestation 18-23 wk 	<ul style="list-style-type: none"> • 37/65 • 4/65 	<ul style="list-style-type: none"> • 383/597 • 572/597
Schwarze et al, ³² Germany	19-26	346 (10.1)	Women with singleton pregnancy. Excluded: women with essential hypertension, diabetes mellitus, autoimmune disease, history of pre-eclampsia, intrauterine growth restriction, intrauterine stillbirth, placental abruption in previous pregnancies, multiple pregnancy, fetal abnormalities	Birth weight < 10th centile	Transabdominal, colour, crossover	<ul style="list-style-type: none"> • Any resistance index > 0.58 • Both resistance indexes > 0.58 • Any resistance index > 0.7 • Both resistance indexes > 0.7 • Any notching • Bilateral notching 	<ul style="list-style-type: none"> • 18/35 • 4/35 • 7/35 • 12/35 • 20/35 • 10/35 	<ul style="list-style-type: none"> • 195/311 • 264/311 • 270/311 • 246/311 • 187/311 • 214/311
Sekizuka et al, ³³ Japan	6-13	135 (7.4)	Low-risk women. Excluded: women with threatened abortions and fibroids	Birth weight < 10th centile (local and gestational values)	Transvaginal, colour + pulsed wave, internal os	Bilateral notching	9/10	10/125
Soutif et al, ³⁴ France	21	315 (10.4)	Primiparous women. Excluded: women with nephropathy, chronic hypertension, diabetes mellitus, systemic disorders, multiple pregnancy	Birth weight < 10th centile (local values)	Unreported route and site, colour + pulsed wave	S/D ratio > 2.6 or any notching	10/33	242/282

continued

Appendix 4A: Patients at low risk or unspecified risk of intrauterine growth restriction (part 6 of 6)

Study, country	Gestation, wk	Total no. of patients (% with intrauterine growth restriction)	Patient group (study design*)	Reference standard for intrauterine growth restriction	Details of index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Subtil et al, ³⁵ France, Belgium	22-24	1186 (1.9) 1186 (10.3)	Women undergoing routine Doppler ultrasonography followed by ASA prescription v. placebo in case of abnormal Doppler findings (randomized controlled trial)	• Birth weight ≤ 3rd centile (local and gestational values) • Birth weight ≤ 10th centile	Unreported route and type, crossover	Resistance index ≥ 0.61 or any notching • Birth weight ≤ 3rd centile • Birth weight ≤ 10th centile	• 11/23 • 45/123	• 935/1163 • 869/1063
Todros et al, ³⁶ Italy	19-24	916 (4.6)	Women with singleton pregnancy, no prepregnancy pathology, no obstetric risk, no chromosomal or structural anomalies	Birth weight < 10th centile (local values)	Unreported route and site, continuous wave + pulsed wave	S/D ratio > 2.7	5/42	820/874
Uludag et al, ³⁷ Turkey	18-20	80 (11.3)	Nonsmokers. Excluded: women with diabetes mellitus, fetal anomalies, multiple pregnancy	Birth weight < 10th centile (unreported data set)	Transabdominal, colour + pulsed waved, unreported site	Bilateral notching	6/9	60/71
Valensise et al, ³⁸ Italy	24	192 (14.6)	Low-risk primiparous women with no current or previous relevant medical history (<i>n</i> = 104). High-risk women with history of pregnancy-induced hypertension, intrauterine growth restriction, intrauterine stillbirth (<i>n</i> = 88). Excluded: women with intrauterine growth restriction on ultrasound screening or oligohydramnios	Birth weight < 10th centile (gestational values)	Unreported route and site, colour	Resistance index > 0.58 (mean)	24/28	149/164
Valensise et al, ³⁹ Italy	24	272 (7.7)	Primigravid women. Excluded: women with history of hypertension, diabetes mellitus, systemic lupus erythematosus, pharmacological induction of ovulation, fetal or chromosomal abnormalities	Birth weight < 10th centile (local values)	Transabdominal, colour + pulsed wave, crossover	Resistance index > 0.58	14/21	239/251
Zimmermann et al, ⁴⁰ Finland	20-24	55 (7.2)	Low-risk women (<i>n</i> = 29) and high-risk women with family or personal history of pre-eclampsia, chronic hypertension or intrauterine growth restriction or intrauterine stillbirth (<i>n</i> = 26) (randomized controlled trial)	Birth weight < 10th centile (local values)	Unreported route, pulsed wave, crossover	Bilateral notching	3/4	24/51

Note: 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 4B; see end of document for references.

Appendix to Cnossen 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

Appendix 4B: Patients at high risk of intrauterine growth restriction (part 1 of 6)

Study, country	Gestation, wk	Total no. of patients (% with intrauterine growth restriction)	Patient group (study design)*	Reference standard for intrauterine growth restriction	Details index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Aardema et al, ⁴¹ the Netherlands	21-22	94 (10.6)	Multiparous women with singleton pregnancy who had a history of hypertensive disorders in previous pregnancy but no current pathology	Birth weight < 10th centile (local, gestational and sex values)	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Pulsatility index ≥ 1.3 • Any notching 	<ul style="list-style-type: none"> • 8/10 • 5/10 	<ul style="list-style-type: none"> • 58/84 • 64/84
Alkazaleh et al, ⁴² Canada	19-23	50 (52.0)	Women with α -fetoprotein > 2.0 multiples of the median and human chorionic gonadotropin > 2.5 multiples of the median	Birth weight < 10th centile (sex and gestational values)	Unreported route, colour + pulsed wave, crossover	Mean pulsatility index > 1.45 or bilateral notching	21/26	17/24
Axt-Flidner et al, ⁴³ Germany	19-26	52 (13.5)	High-risk women with singleton pregnancy: history of pre-eclampsia, intrauterine growth restriction, intrauterine stillbirth, abruptio	Birth weight < 10th	Transabdominal, colour, crossover	<ul style="list-style-type: none"> • Any resistance index > 0.58 • Both resistance indexes > 0.58 • Any resistance index > 0.7 • Both resistance indexes > 0.7 • Any notching • Bilateral notching 	<ul style="list-style-type: none"> • 7/7 • 5/7 • 3/7 • 2/7 • 5/7 • 5/7 	<ul style="list-style-type: none"> • 21/45 • 36/45 • 41/45 • 44/45 • 23/45 • 36/45
Caforio et al, ⁶ Italy	18-20 22-24	335 (15.2) 335 (33.4)	Women with chronic hypertension, diabetes mellitus, autoimmune disease, systemic lupus erythematosus, renal disease; history of stillbirths, fetal growth restriction, pre-eclampsia, habitual abortion	(a) Birth weight < 1750 g (b) Birth weight < 2500 g	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Resistance index > 90th centile • Gestational age 18-20 wk • Gestational age 22-24 wk 	<ul style="list-style-type: none"> a) 36/51 b) 68/112 a) 44/57 b) 73/120 	<ul style="list-style-type: none"> a) 196/284 b) 165/223 a) 202/277 b) 166/215
Caruso et al, ⁴⁴ Italy	18-24	28 (10.7) 28 (39.0)	Women with antiphospholipid syndrome	<ul style="list-style-type: none"> • Birth weight < 10th centile (local values) • Birth weight < 1750 g 	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Resistance index > 90th centile • Birth weight < 10th centile • Birth weight < 1750 g 	<ul style="list-style-type: none"> • 2/3 • 9/11 	<ul style="list-style-type: none"> • 19/25 • 17/17
Caruso et al, ⁴⁵ Italy	23-24	42 (9.5) 42 (42.0)	Women with chronic hypertension and singleton pregnancy. Excluded: women autoimmune disease, fetal anomalies, Rhesus isoimmunisation	<ul style="list-style-type: none"> • Birth weight < 10th centile (local values) • Birth weight < 2500 g 	Transabdominal, colour, crossover	<ul style="list-style-type: none"> • Mean resistance index > 90th centile • Birth weight < 10th centile • Birth weight < 2500 g 	<ul style="list-style-type: none"> • 4/4 • 14/18 	<ul style="list-style-type: none"> • 27/38 • 23/24

continued

Appendix 4B: Patients at high risk of intrauterine growth restriction (part 2 of 6)

Study, country	Gestation, wk	Total no. of patients (% with intrauterine growth restriction)	Patient group (study design)*	Reference standard for intrauterine growth restriction	Details index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Coleman et al, ⁴⁶ New Zealand	22-24	116 (26.7)	Women with essential and secondary hypertension, renal disease, systemic lupus erythematosus, antiphospholipid syndrome, previous pre-eclampsia or placental abruption. Excluded: women with multiple pregnancy, fetal abnormalities	Birth weight < 10th centile (local values)	Transabdominal, colour, crossover	<ul style="list-style-type: none"> • Any resistance index > 0.58 • Both resistance indexes > 0.58 • Any resistance index ≥ 0.7 • Both resistance indexes ≥ 0.7 • Any notching • Bilateral notching • Any resistance index > 0.58 and any notching • Any resistance index > 0.7 and any notching • Both resistance indexes > 0.7 and any notching 	<ul style="list-style-type: none"> • 26/31 • 14/31 • 17/31 • 8/31 • 19/31 • 11/31 • 19/31 • 15/31 • 8/31 	<ul style="list-style-type: none"> • 33/85 • 67/85 • 62/85 • 81/85 • 59/85 • 76/85 • 59/85 • 69/85 • 82/85
Degani et al, ⁴⁷ Israel	15	124 (31.5)	Women with singleton pregnancy, accurately dated, previous small-for-gestational-age infant, and no chromosomal or structural anomalies	Birth weight < 10th centile (gestational values)	Transabdominal, colour + pulsed wave, unreported site	Mean pulsatility index > 1.12	9/39	68/85
Ferrier et al, ⁴⁸ Australia	19-24	51 (11.8)	Women with renal disease other than diabetic nephropathy	Birth weight < 10th centile (local and gestational values)	Transabdominal, colour, crossover	Resistance index > 90th centile or notching on placental side or highest value if midline	5/6	36/45
Frusca et al, ⁴⁹ Italy	24	56 (23.2)	Women with history of pre-eclampsia and normal blood pressure after that pregnancy	Birth weight < 10th centile	Transabdominal, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Resistance index > 0.58 • Any notching • Bilateral notching and resistance index > 0.58 	<ul style="list-style-type: none"> • 11/13 • 11/13 • 6/13 	<ul style="list-style-type: none"> • 30/43 • 33/43 • 41/43
Geipel et al, ⁵⁰ Germany	18-24	256 (17.6)	Women with dichorionic twins. Excluded: women with fetal anomalies, preterm prelabour rupture of membranes, unclear chorionicity, unavailable outcome	Birth weight < 10th centile (twin reference ranges in local population)	Unreported route and type, crossover	<ul style="list-style-type: none"> • Resistance index > 95th centile (singleton reference) • Resistance index > 95th centile (twin reference) • Resistance index > 95th centile + any notching (twin reference) • Any notching • Bilateral notching 	<ul style="list-style-type: none"> • 4/45 • 12/45 • 11/45 • 16/45 • 4/45 	<ul style="list-style-type: none"> • 207/211 • 187/211 • 198/211 • 184/211 • 201/211
Geipel et al, ¹¹ Germany	18-24	114 (14.0)	Patients who underwent intracytoplasmic sperm injection, women with singleton pregnancy	Birth weight < 10th centile (local values)	Unreported route, colour, crossover	Bilateral notching + mean resistance index > 0.55 or unilateral notching + mean resistance index > 0.65 or no notching + mean resistance index > 0.7	7/16	78/98

continued

Appendix 4B: Patients at high risk of intrauterine growth restriction (part 3 of 6)

Study, country	Gestation, wk	Total no. of patients (% with intrauterine growth restriction)	Patient group (study design)*	Reference standard for intrauterine growth restriction	Details index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Geipel et al, ¹¹ Germany	18-24	32 (18.8)	Patients who underwent intracytoplasmic sperm injection, women with twin pregnancy	Birth weight < 10th centile (local values)	Unreported route, colour, crossover	Bilateral notching only	4/6	22/26
Geipel et al, ¹¹ Germany	18-24	32 (21.8)	Women with twin pregnancy (control group of intracytoplasmic sperm injection)	Birth weight < 10th centile (local values)	Unreported route, colour, crossover	Bilateral notching only	3/7	20/25
Haddad et al, ⁵¹ France	First at mean 23.8	48 (18.7)	Women given ASA therapy because of poor previous outcome, pre-eclampsia, eclampsia, HELLP syndrome, abruption, intrauterine growth restriction, intrauterine stillbirth	Birth weight < 10th centile (local and gestational values)	Unreported route and site, continuous waved	<ul style="list-style-type: none"> • Ratio of diastolic to systolic velocity < 10th centile unilateral • Ratio of diastolic to systolic velocity < 10th centile unilateral or diastolic notching • Unilateral diastolic notching 	<ul style="list-style-type: none"> • 7/9 • 8/9 • 7/9 	<ul style="list-style-type: none"> • 24/39 • 21/39 • 28/39
Harrington et al, ¹⁶ United Kingdom	19-21	170 (10.2)	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	Birth weight < 5th centile (local values)	Transabdominal, 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)	11/26	115/144
Hershkovitz et al, ⁵² United Kingdom	24	88 (26.1)	Women with chronic hypertension, history of severe pre-eclampsia, thrombophilia	Birth weight < 10th centile (local, gestational and sex)	Unreported route, colour + pulsed wave, crossover	<ul style="list-style-type: none"> • Pulsatility index (mean) > 95th centile or any notching • Pulsatility index (mean) > 95th centile or bilateral notching 	<ul style="list-style-type: none"> • 17/23 • 12/23 	<ul style="list-style-type: none"> • 49/65 • 55/65
Konchak et al, ⁵³ United States	17-22	103 (17.4) 103 (13.5)	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	<ul style="list-style-type: none"> • Birth weight < 10th centile (local values) • Birth weight < 2500 g 	Transabdominal, colour + pulsed wave, crossover	Birth weight < 10th centile a) Unilateral notching b) Resistance index \geq 0.7 (95th) Birth weight < 2500 g a) Unilateral notching b) Resistance index \geq 0.7 (95th)	<ul style="list-style-type: none"> a) 3/18 b) 3/18 a) 4/14 b) 5/14 	<ul style="list-style-type: none"> a) 79/85 b) 77/85 a) 84/89 b) 83/89
Le Thi Huong et al, ⁵⁴ France	2nd trimester	100 (18.0)	Women with systemic lupus erythematosus, antiphospholipid syndrome	Birth weight < 10th centile (gestational values)	Unreported route and type, crossover	Any notching	3/15	70/85

continued

Appendix 4B: Patients at high risk of intrauterine growth restriction (part 4 of 6)

Study, country	Gestation, wk	Total no. of patients (% with intrauterine growth restriction)	Patient group (study design)*	Reference standard for intrauterine growth restriction	Details index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Nagtegaal et al, ⁵⁵ Australia	18-22	182 (19.8) 182 (12.1)	Women with previous pre-eclampsia, intrauterine growth restriction, placental abruption, recurrent miscarriages, unexplained stillbirth, chronic hypertension, type 1 diabetes mellitus, thrombophilia, positive family history of pre-eclampsia	<ul style="list-style-type: none"> • Birth weight < 10th centile (local and gestational values) • Birth weight < 5th centile 	Unreported route and site, colour + pulsed wave	Mean resistance index \geq 0.58 + any or no notching or mean resistance index < 0.58 + bilateral notching <ul style="list-style-type: none"> • Birth weight < 10th centile (local and gestational values) • Birth weight < 5th centile 	<ul style="list-style-type: none"> • 23/36 • 14/22 	<ul style="list-style-type: none"> • 42/146 • 47/160
Soregaroli et al, ⁵⁶ Italy	24	282 (18.0)	Women with high-risk pregnancy (history of gestational hypertension, pre-eclampsia, intrauterine growth restriction, intrauterine stillbirth, chronic hypertension, autoimmune disease, renal disease) Excluded: women with multiple pregnancy, fetal chromosomal anomalies, pregnancy complications < 24 wk	Birth weight < 10th centile (local and gestational values)	Transabdominal, colour, crossover	Resistance index > 0.6 or bilateral notching	40/50	187/232
Vainio et al, ⁵⁷ Finland	12-14	72 (5.6)	Women at high risk for pre-eclampsia. Excluded: women with gestational age outside study limits, asthma, allergy to ASA, peptic ulcer, prostaglandin inhibitor therapy, < 10 d of investigation	Birth weight < 10th centile (local values)	Transvaginal, colour, uterocervical junction	Bilateral notching	3/4	28/68
Valensise et al, ⁵⁸ Italy	22 and 24	16 (43.7)	Women with chronic hypertension	Birth weight < 10th centile (local and gestational)	Unreported route, continuous wave, crossover	Resistance index > 0.58 (+2 SD) + notching	7/7	8/9

continued

Appendix 4B: Patients at high risk of intrauterine growth restriction (part 5 of 6)

Study, country	Gestation, wk	Total no. of patients (% with intrauterine growth restriction)	Patient group (study design)*	Reference standard for intrauterine growth restriction	Details index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
van den Elzen et al, ⁵⁹ the Netherlands	7-11	320 (10.0)	Women > 35 yr at 20 wk with diastolic blood pressure < 85 mm Hg, no history of hypertension, cardiovascular disease or diabetes who have viable singleton pregnancy < 11 wk	Birth weight < 10th centile (local, sex and gestational values)	Unreported route, colour, crossover	Gestational age 7-11 wk	• 22/32	• 70/288
	12-13	341 (9.4)				• Pulsatility index > 1.52 (25th centile)		
	23-27	351 (9.6)				• Pulsatility index > 1.78 (50th centile)		
						• Pulsatility index > 2.07 (75th centile)		
						Gestational age 12-13 wk		
						• Pulsatility index > 1.24 (25th centile)		
						• Pulsatility index > 1.41 (50th centile)		
						• Pulsatility index > 1.66 (75th centile)		
						Gestational age 23-27 wk		
		• Pulsatility index > 0.96 (25th centile)						
		• Pulsatility index > 1.09 (50th centile)						
		• Pulsatility index > 1.23 (75th centile)						
Venkat-raman et al, ⁶⁰ United Kingdom	16-18	164 (12.8)	Women with recurrent miscarriage and antiphospholipid syndrome (no systemic lupus erythematosus or thromboembolic disease)	Birth weight < 10th centile (local, sex and gestational values)	Unreported route, colour, crossover	Gestational age 16-18 wk	a) 16/21	a) 81/143
	22-24	163 (13.5)				a) Any notching		
						b) Bilateral notching		
						Gestational age 22-24 wk		
		a) Any notching						
		b) Bilateral notching						
		b) 5/21						
		a) 120/142						
		b) 133/142						

continued

Appendix 4B: Patients at high risk of intrauterine growth restriction (part 6 of 6)

Study, country	Gestation, wk	Total no. of patients (% with intrauterine growth restriction)	Patient group (study design)*	Reference standard for intrauterine growth restriction	Details index test	Index test cutoff, centile or absolute threshold	Sensitivity, TP/(TP + FN)	Specificity, TN/(FP + TN)
Yu et al, ⁶¹ United Kingdom	22-24	351 (8.8) 351 (23.6) 351 (6.3) 351 (17.9)	Twin pregnancies, 2 live fetuses, no fetal abnormality, no twin transfusion syndrome	<ul style="list-style-type: none"> • Birth weight < 5th centile both twins (local, gestational singleton reference) • Birth weight < 5th centile 1 twin • Birth weight < 3rd centile both twins • Birth weight < 3rd centile 1 twin 	Transvaginal, colour + pulsed wave, level of internal os	<ul style="list-style-type: none"> • Birth weight < 5th centile both twins (local, gestational singleton reference) a) Mean pulsatility index > 1.5 (95th centile) b) Bilateral notching • Birth weight < 5th centile 1 twin a) Mean pulsatility index > 1.5 (95th centile) b) Bilateral notching • Birth weight < 3rd centile both twins a) Mean pulsatility index > 1.5 (95th centile) b) Bilateral notching • Birth weight < 3rd centile 1 twin a) Mean pulsatility index > 1.5 (95th centile) b) Bilateral notching 	<ul style="list-style-type: none"> a) 3/33 b) 1/31 a) 5/83 b) 5/83 a) 3/22 b) 1/22 a) 4/63 b) 5/63 	<ul style="list-style-type: none"> a) 305/320 b) 309/320 a) 255/268 b) 261/268 a) 314/329 b) 318/329 a) 274/288 b) 281/288

* Cohort study unless otherwise stated.

Note: FN = false negative, FP = false positive, FPR = false positive rate, MoM = multiples of the median, SD = standard deviation, TP = true positive, TN = true negative.

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