Supplement C
Outcometabeller vid hypertonisjukdomar under graviditet

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1. Blodtrycksmätare

Treatment of preeclampsia/eclampsia. Literature search 160225 and 180130 **BP device** **Outcome variable: Automatic vs auscultatory**									
Author **Year** **Country**	**Study design**	**Number of studies/ patients**	**Withdrawals Dropouts**	**Results**	**Comments**	**Problems**			**Quality**
Bello et al 2018 USA	SR	41 >200 pregnant women	na	I=Ambulatory Home measurement C=Clinic measurement p=ns if validated devices	28 devices PRISMA 2.758 studies initially Devices should be tested before clinical use/Sphygmanometer	+	+	+	High
Davis et al 2015 Australia	Observational	340 I=170 C=170	na	I1= 85 HT Ascultatory hybrid sphygmanometry I2= 85 HT Automated oscillometric device C1= 85 normotensive Auscultatory sphygmanometry C2= 85 normotensive Automated oscillometric device p=0.001	Autom hybrid blood-pressure measurement (UM 101, A&D CompanyLTD) more accurate than automated oscillometric device (Omron HEM-907) BHS protocol	+	+	-	Moderate
Lan et al 2014 Australia	Observational	89	na	I= Mercury sphygmanometry C=Automatic device outpatient p=ns	Automated blood-pressure measurement = sphygmanometry Patients their own control Omron HEM-2700 Ante- or postpartum, risk-patients, PE Difference no clin significance	+	?	+	Low

I=Intervention, C=control, HT=hypertensive, PE=preeklampsia, na=not applicable

2. Protein/kreatinin

Treatment of preeclampsia/eclampsia. Literature search 160225 and 180130 **Protein/creatinine** **Outcome variable: Spot/24h**									
Author, Year, Country	**Study design**	**Number of studies/ patients**	**With-drawals Dropouts**	**Results**	**Comments**	**Problems**			**Quality**
Stout et al 2015 USA	SR	7/87 studies n=410		I=12h urine sample C=24h urine sample p=ns	12h = 24h proteinuria	+	+	+	High
Cade et al 2015 Australia	Prospect ive cohort	181	None	I=spot ACR C=spot PCR p= ns	Patients are their own control. ACR 13.4mg/mmol correspond PCR 30 mmol	?	-	?	Low
Correa et al 2017 Canada/UK	Prospect ive cohort	338	35	I = Multistix Visual method C = Multistix 10SG/Clinitec 50 Automated method C = Chemistrip Automated method p<0.001	Automated more sensitive than visual reading	+	+	+	High
Haghigi et al 2016 Iran	Prospect ive cohort	120		I=4 h PCR I=8 h I= 12 h day I= 12 h night C=24 h p<0.001	4h sample adequate compared to 24 h sample. Spot PCR sufficient	?	-	?	Low
Valdes et al 2016 Chile	Prospect ive cohort	72	Not stated	I=24 h urine sample prot C=Spot PCR p=ns	42 PE women	+	?	+	Moderate
Verdonk et al 2014 Netherlands	Prospect ive cohort	112	7	I=24 h prot C=Spot PCR p=ns	Spot=24h Prot/crea samples tested 08.00, 12.00 and 17.00	+	+	?	Moderate
Waugh J et al 2017 UK	HTA Prospect ive cohort	959		I=Spot PCR I2= Spot ACR C=24 h urine prot ratio p=ns spot vs 24h	417 PE ACR more sensitive than PCR	+	+	+	High

Wilkinson et al 2013 Ireland	Prospect ive cohort	89 (132 samples)	7	I1=PCR I2=ACR C=24h collection p = ns	Cut-off point significant proteinuria PCR <20mg/mmol ACR <2.5 mmol	+	?	+	Moderate
Lee AM et al 2014 USA	Retrospe ctivecoh ort	238	88	I= protcinconentration C= Total U/prot level p=ns	Comparison of methods Prot concentration 0.1mg/mL Equivalent to 300 mg total protein/24 h Urine sample	+	+	+	High
Stout et al 2013 USA	Retrospe ctive cohort	369 Suspected PE	13	I= 24 h urine sample protein C=Spot PCR P???	HDP > 20gw. Significant proteinuria 144/356 PE were diagnosed earlier with a spot sample	+	+	+	High
Amin et al 2014 India	Case control	102	NA	I= 24 h urine sample C= spot PCR ns (prediction of significant proteinuria)	HDP after 20 gw. Patients are their own control.	?	-	?	Low
Demirci et al 2015 Turkey	Prospect ive Case control	264	?	I=PE (211) C=nonPE (53) Spot PCR=24h prot/crea Positive correlation r= 0.758	Spot PCR = 24 h sample	-	-	-	Low

HTA=Health Technology Assesment, alb=albumin, crea=creatinine, HDP=hypertensive disease of pregnancy, U=urine, PCR=protein creatinine ratio, ACR=albumin creatinine ratio

3. Outcome Riskfaktorer

Treatment of preeclampsia/eclampsia Literature search 160225 and 180130 **Riskfactors for eclampsia or preeclampsia** **Outcome variable: Preeclampsia**								
Author, Year, Country	**Study design**	**Number of studies/ patients**	**With-drawala – dropouts**	**Results**	**Comments**	**Problems**		**Quality**
				Riskfactors				
Bartsch et al 2016 Canada	SR	92 25356688 high risk pregnancies		I=PE (one or more riskfactors) C=nonPE	Riskfactors = APS, history of PE, chron HT, GDM, BMI >30, IVF	+	+	+	High
Jaskolka D et al 2017 Canada	SR Meta-analysis	22 studies 3.163.735		I=Fetal sex male C= Fetal sex fem p=ns	22 studies included 1950 - 2015 non-Asian population p0.33 Low quality studies	+	?	-	Moderate
Sibai et al 1998 USA	RCT	763 pregnancies		I=Proteinuria at baseline 81 C= Non proteinuria 682 p= ns	Secondary analysis of RCT Aspirin vs placebo. Risk for PE if proteinuria or not in early pregnancy	?	-	-	Low
Block-Abraham et al 2014 USA	Prospec tive Nested Cohort	614 Riskpopulation		I=PE 59 (9.6%) C=nonPE 555 (90.4%) p NA	More serious riskfactors (APS, history of PE, chron HT, GDM, BMI >30, IVF) in the group developing PE.	+	?	-	Moderate Low
Egeland G M et al 2016 Norway	Prospec tive cohort	13.217		I1=PE I2=GH C=non hypertension	Family history cardiovascular riskfactors increases risk PE Physical activity less risk preterm PE in nulliparous	?	?	?	Moderate
Grobman WA et al 2018 USA	Prospective cohort	10.038	568	I1=Race I2=Psychosocial stress O=PE/nonPE 1. p<0.05	Non-hispanic black women higher risk	-	+	?	Moderate
Adane A et al 2017 Australia	Retrosp ective cohort	14.247 Complete 2.914	11.333	I=HDP I2=nonHDP	Changes in BMI related to GH				Low

Ankumah et al 2014 USA	Retrosp ective cohort	776 mild chron HT	17	I= (>140/90 mmHg at enrollment) PE 66/221 (29.9%) C=(<140/90 mmHg at enrollment) 101/478 (21.1%) p <.001	Primary composite (severe PE, perinatal death, Abruption, <35 gw) Mild HT i.e. well treated at beginning of pregnancy had a lower risk of PE. 49 resp 52% in both groups received aspirin	+	?	?	Moderate Low
Boyd HA et al 2013 Denmark	Retrospective cohort	48.128		I1=early onset PE < gw 34 I2=intermediate onset PE at gw 34- 36 I3=Late onset PE gw>36	Family history PE Maternal family factors related to early onset PE. Late onset related to environmental factors 25.2 times recurrent PE risk if early onset, 1.3 times risk if late onset	?	-	-	Low
Ekiz et al 2015 Turkey	Retrospective Observational	157 ≥1+ proteinuria > gw20		I= 53 PE C=104 nonPE p=0.001	PE in 1/3 of women with ≥1+ proteinuria > gw20	+	?	-	Moderate /Low
Esakoff et al 2016 USA	Retrosp ective cohort	n=143093 PE and GH		I= 1719 eclampsia C=non eclampsia	Prediction for eclampsia: Race, nulliparity, <20 yrs, preterm Chron HT less risk eclampsia	+	?	-	Moderate / Low
Haslinger C et al 2016 Switzerland	Retrospective cohort	36.328 cohort 2.193 eligible		I=>45 years C=30 years O=PE OR 5.4 95% 3.1-9.5	2066 vs 127	-	-	-	Low
Kuper SG et al 2016 USA	Retrospective cohort	755	16	I=creatinine level < 1.2 mg/dL (739) C=NA	PE < gw34	+	+	-	Moderat e
Lisonkova et al 2013 USA	Retrosp ective Register	456.668	27.443 5.7%	I=singletons PE C=non PE	Different riskfactors for early- and late-onset PE affecting care Age, race, chron HT, diabetes	+	?	?	Low
Pettit F et al 2015 Australia	Retrospective cohort	4.463	3.767	I=Early onset PE <34 GW I2=Preterm PE 34-37 gw I3= Term PE >37 gw	Maternal and neonatal morbidity	+	?	-	Moderate / Low
Rasmussen S et al 2017 Norway	Retrosp ective cohort	1967 – 2012 742.980		I=Premature birth history without PE C=Term pregnancy OR 3.5 (95% CI 3.0-4.0)	Preterm PE	+	?	?	Low

Rodriguez-Lopez M et al 2017 Sweden	Retrospective cohort	2001-2010 719.061	92.461	I=PE 24.023 C=Non PE/Eclampsia	No Riskfactors alone for PE Combination of riskfactors better discrimination accuracy eg obesity, multiple pregn especially with chron HT				Low
Fox et al 2014 USA	Case control	532 twin-pregnancies	10 Chr HT 9 monoamnion	I= with PE C= without PE	Riskfactors PE in twin pregnancy =eggdonation, prepregnancy obesity	+	?	-	Low
				Vitamin D/Calcium					
He et al 2016 China	Meta-analysis	Until 15 January 2015 15 studies		I=Ca I2 Zn I3=Mg p <0.005	Low Ca Zn Mg higher risk PE China, India, Korea, Turkey	?	?	+	Moderate / Low
Gernand et al 2017 USA	RCT	839 women	17	I= 25(OH)Vit D < 25 nmol/L I2= 25(OH)Vit D < 30 nmol/L I3= 25(OH)Vit D < 50 nmol/L I4= 25(OH)Vit D ≥75 nmol/L C=Placebo aRR 2.40 95%CI 1.04-5.56 if <30 nmol/L	Vit D Status and risk for PE and preterm birth in high risk women	+	?	-	Moderate /Low
Kiely ME et al 2016 Irland	Prospective cohort	1768		I= <30 nmol/L Vitamin D level I2=<50 nmol/L I3=>75 nmol/L 3. OR 0.64 95% CI 0.43-0.96	PE SGA Protective association if > 75 nmol/L regarding composite outcome PE SGA	-	?	-	Low
Boyle VT et al 2016 New Zealand	Prospective cohort	2.065	355	I=<75 nmol/L Vitamin D C>75 nmol/L p=ns	1.710 No difference regarding PE,	+	-	+	Moderate
Burris et al 2014 USA	Prospective cohort	2128	537	I=PE C=GH C2=non HT ns	Vit D level <10 gw	+	?	+	Moderate
Flood-Nichols et al 2015 USA	Retrospective cohort	2014235 nullipara 310	75	I=vit D<30 ng/mL C=Vit D>30ng/mL ns	PE	+	+	+	Moderate

Achkar et al 2015 Canada	Case control	PE 169 C 1975	7076	I=Vit D 47.2+-17.7 C=Vit D 52.3 +-17.2 P=.0002	VitD deficiency riskfactor for PE	+	?	?	Moderate
Baca KM et al 2016 USA, Canada	Case-cohort study	2.327 random sample of 12.861 eligible		I1= <25nmol/L I2= 25-49,9 nmol/L I3=50-74,9 nmol/L I4=>75 nmol/L For value <25nmol/L RR 2.4 95%CI 1.2-4.8 PE RR 3.2 95%CI 1.3-7.9 Severe PE RR 2.4 95%CI 1.1-5-1 Mild PE	PE 650 Secondary analysis	+	?	-	Low
				Folic acid					
Wen et al 2016 Canada	Prospec tive cohort	7.669 2006-2008.		I= Folic acid ≥1.0mg(7.265) C=no folic acid (404) OR 0.17 95%CI 0.03-0.95 in high risk women	lab analysis n=902	+	-	?	Low
				Pregnancy interval					
Cormick G et al 2016 Argentina	SR Meta- analysis	4		I1=< 2yrs interval I2=2-4 yrs interval pregnancy I3=>4 yrs aOR 1.10 95%CI 1.02-1.19	Meta analysis of 2 studies PE. PRISMA All retrospective cohorts, high income countries. Low power.	+	+	+	High
Hanley GE et al 2017 Canada	Retrosp ective cohort	38.178		I=0-5 I=6-11 I=12-17 I=18-23(ref I=24-59 I=>60 mo OR 1.31 95% CI 1.09-1.58 if >60 mo	Inter Pregnancy interval in relation to PE Long intervals increased risk	?	?	?	Low
Howe L et al 2017 USA	Retrospective case-series	171		I1= <24 months interpregnancy interval (40) I2=24-48 months (105) I3>48 months (26) p = ns	Bloodpressure in subsequent pregnancy after PE	?	-	-	Low
Klemetti R et al 2016 Finland	Retrospective cohort	228348		I1=PE I2=GH C1= nonPE	228348 First-time mothers Threshold age according to significant OR	+	+	+	High

				C2=nonGH 1 .>38 yrs OR 1.48 95% 1.12-1.96 2. >33 yrs OR 1.14 95% CI 1.03-1.27					
Lean SC et al 2017 UK	SR Meta-analysis	74		I=≥35 yrs C = <35 yrs OR 1.99 CI 95% 1.65-2.36	Primary outcome was stillbirth. PE included among other adverse outcomes	+	+	+	High
				CVB/ART					
Basaran A et al 2016 USA	SR Meta- analysis	9		I=CVB C1=AC+non invasive C2=Non invasive procedure p=ns	Pooled values Limited power due to heterogenecity	+	+	+	High
Blazquez A et al 2016 Spain	SR Meta- analysis	11		I= Egg donation C=IVF OR 3.12	PE. Cohort studies only	+	+	+	High
Letur H et al 2016 France	Prospecive cohort	580	127	I=Egg donation (169) C=ART (284 p=0.001		+	+	?	Moderate
Savasi VM et al 2016 Italy	SR	2010 – Nov 2015 6		I=Egg donation C=IVF aOR 4.0 (95% CI 1.5-11.9)	Egg Donation and PE	?	-	+	Low
Schwarze et al 2017 Chile	SR Meta- analysis	6 cohort studies		I=Egg donation C=IVF RR 2.62 (95%CI 2.13-3.21)	Egg Donation and PE Singleton pregnancies	+	+	+	High
Thomopoulos et al 2017 Greece	SR Meta- analysis	66 7.038.029 203.375 ART		I=ART C=Spontan pregnancy P=0.005	Risk PE and ART	+	+	+	High
				Obstructive Sleep Apnea (OSA)					
O'Brien LM et al 2014 USA	Prospec tive cohort	181 hypertensive pregnant women 70 healthy controls	2+2	I=21/51 hypertensive pregnancies C=3/16 Non hypertensive O=OSA p=0.05	181 eligible Small study	+	?	?	Moderate

Bin Y S et al 2016 Australia	Retrosp ective cohort	636.277 pregnancies		I=pregnancies and sleep apnea 519 C= non sleep apnea 635.708	Risk gestational hypertension	+	-	+	Moderate
Bourjeily G et al 2017 USA	Retrosp ective cohort	1963 vs1.577.632		I=OSA C=Non OSA OR 2.22 95% CI 1.94-2.54	PE				Low
Louis J et al 2014 USA	Retrosp ective cross- section al	55.781.965 pregnant hospital discharges		I=OSA C=Non OSA PE OR2.5 95%CI 2.2-2.9	Severe maternal-Infant morbidity-Mortality				Low
				BMI/Weight-gain					
Hannaford K E et al 2017 USA	Prospective cohort	Decenber 2008 – April 2012 1200		I Adequate weight gain I= Inadequate I= Excessive p=ns	Secondary analysis Riskfactor PE	+	?	?	Moderat e
Durst et al 20165 USA	Retrosp ective cohort	10196 Singleton live birth		I1=overweight I2=obese I3=morbidly obese C=normal weight 1. OR 1.4 95% CI 1.0-2.1 2. OR 2.0 95%CI 1.4-2.8 3. OR 2.0 95% CI 1.3-2.9	Increased risk for late onset PE	-	?	+	Low
Knight-Agarwal CR et al 2016 Australia	Retrospective cohort	14857		I1= 1-<3 BMI units I2= >3 BMI units C= No BMI change 1.OR 3.696 95% 0.54-72.696 2.9.642 95% 1.517-186.621	14857 Interpregnancy BMI change				Low
Lucovnik et al 2014 Slovenia	Retrosp ective cohort	2046 twins 6138 singleton		I=BMI C1=BMI change C2=Singleton C3=Twin	PE and Gestational diabetes related to high BMI Prepregnancy high BMI is a stronger riskfactor for PE than weight gain during pregnancy Unclear data, interpretation difficult	?	-	-	Low

Chandrasekaran et al 2015 USA	Case control	695 ≥30 BMI before 18 gw		I=Excessive weight gain C1=normal weight gain C2=under weight gain p <0.001	GHT Obese with excessive weigh gain increased risk I= 2x ökad GHT jmf C1	+	?	?	Low
				DIVERSE					
Fazzi C et al 2017 USA	SR	26		I=sedentary behaviour C= Non sedentary pregnant/ non pregnant p= ns	PE Mixed population men, women pregnant Mostly self report of behavior Only one RCT PRISMA	+	+	+	High
Easter et al 2016 USA	Prospec tive cohort	2607		I=Urinary tract infection C=no UTI p<0.001	PE	+	?	?	Low

4. ASA-profylax

Treatment of preeclampsia/eclampsia Literature search 160225 and 180130 **ASA prophylaxis** **Outcome variable: Preeclampsia**								
Author, Year, Country	**Study design**	**Number of studies/ patients**	**With-drawals - dropouts**	**Results**	**Comments**	**Problems**		**Quality**
SYSTEMATIC REVIEWS and META-ANALYSIS								
Askie LM et al 2007 Australia	Meta analysis	31 RCT/ 32217		I1= ≤ 75 mg ASA/dipyridamole and/or heparin, ozagrel I2= > 75 mg ASA C1= placebo C2= none 10% reduction PE p=.004 and 10% preterm birth < gw 34 p=.011	PARIS study 31 RCT (115 from start (Perinatal Antiplatelet Review of International Studies)	+	+	+	High
Bujold E et al 2009 Canada	SR Meta-analysis	1317		I1= ≤ 16 gw 0.5mg/kg/d, or 75 mg ASA (n=129) I2= 17-19 gw 100 mg ASA (n=104) I3= ≥ 20 gw 50, 60, 75, 100 mg (n=464), 150 mg (n= 560) C= no or placebo ≤ 16 gw RR 0.48;95%CI 0.33-0.68 17-19 gw RR 0.55;95%CI 0.17-1.76 ≥ 20 gw RR 0.82;95% CI 0.62-1.09	9 trials Outcome PE. Significant reduction	+	+	+	High
Coomarasamy A et al 2001 UK	Meta-analysis	332 5 finally		I= ASA 60-100mg/d C=Placebo or none O=PE OR 0.55 95%CI 0.32-0.95	Abnormal a.uterine Doppler Late inclusion gw 17-24	+	+	?	Moderate /High

Gan J et al 2016 China	SR Meta-analysis	2097 21 finally		I= ≤ 100 mg ASA C=Placebo or no treatment O= PE East-Asian vs PE Non East-Asian p=ns O= IUGR East-Asian vs PE Non East-Asian OR 0.36 ;CI 0.20-0.67 vs OR 0.85;CI 0.41-1.77	PRISMA method 21 studies included after 1990 100 mg= 4061 <100mg 14.179 Included gw 12-43 (Wide range)	+	+	+	Moderate
Henderson et al 2014 USA	SR Evidence Synth 112, USPSTF	27	NA	I=50-150mg ASA C=Placebo or no treatment 13 studies risk for PE RR 0.76;CI 0.62-0.95 n=12.184 21 studies studied harm maternal neonatal ns, starting before or after w 16 (9 vs 4 studies) High risk pregnancy advantage to use Aspirin	544 studies initially, 75 of these reviewed fulltext 1.reduced maternal adverse outcome? 2.Prevention PE? 3.Matenal or fetal harm? 6 studies 60mg, 9 studies 100mg 1 study 150mg (see Yu n=276)	+	+	+	High ska vara +++
Lefevre ML 2014 USA	SR USPSTF Recommendation/Guideline				Summering av Henderson				
Meher et al 2017 UK	SR	31 32.217 patients		I= <16gw Low dose ASA C=≥16gw Low dose ASA p=ns	No difference in outcome For doses See PARIS-study	+	+	+	High
Roberge S et al 2013 UK Canada	SR Meta-analysis	42 studies		I1=≤150mg ASA ≤v16 with/without dipyridamole 300mg I2=≤150mg ASA >gw 16 with/without dipyridamole 300mg C=Placebo or no treatment O=PE p<.01 O= severe PE p<.01	Early and late start of low dose ASA on risk for perinatal death and adverse perinatal outcome PRISMA 27.222. Mix of doses. 9 studies ≥100 mg ASA	+	+	+	High
Roberge S et al 2017 UK Canada	SR Meta-analysis	45 studies 20.909		I1=≤100 mg ASA ≤ 16 gw I2=≤100 mg ASA > 16 gw C= Placebo/no treatment P<.001 PE P<.009 severe PE P<.001 IUGR	PE, Severe PE, IUGR Dose-respons effect 50-100mg No effect after 16 gw, just one study evaluates 150mg (Yu 554 patients) Secondary analysis 100 mg vs 60 mg	+	+	+	High
Roberge S et al	Meta-analysis	3 studies		I= 60mg ASA< 17 gw	PE and SGA	+	?	+	Moderate

2016 UK, USA, Canada				C= no treatment p=ns RR 0.93;CI 0.75-1.15	≥350 participants in each study Only 60 mg studied				
Roberge S et al 2018 UK	SR Meta-analysis	20 studies 12.585		I1=≥100 mg ASA ≤gw16 I2=≥100mg ASA >gw16 I3=<100 mg ASA ≤gw16 I4=<100 mg ASA ≤gw16 C=Placebo/no treatment p=ns	Risk patients severe PE. Meta analysis on the effect of dose and gestational age on the risk for placental abruption or antepartum haemorrrhage Two studies150mg (93 Rolnik 2017 and 554 patients Yu 2003)	+	+	+	High
Roberge S et al 2017 Canada, UK	SR Meta-analysis	16		I1=<100 mg ASA ≤gw16 I2=≥100mg ASA ≤gw16 I3=<100 mg ASA >gw16 I4=≥100 mg ASA ≤gw16 C=placebo / no treatment 2. RR 0.33 95% 0.19-0.57 preterm PE 4. RR 0.22 95% 0.07-0.66	Meta-analysis on the effect of dose and gestational age on the risk for preterm and term PE 18.907. Eight studies good quality Yu 27 PE/276 pat	+	+	+	High
Xu et al 2015 China	SR	29 studies 21.403		I=ASA 50-150mg/dipyridamole C=Placebo/no treatment/vit E O= PE P<.001 Start < gw16 p=.00001 Start ≥ gw 16 p=.02	Countries not reported 150mg in 2 studies only 554+560 start 22-24 gw One study dipyridamole+ ASA 150mg start not reported	-	+	+	Moderate
RCT and META-ANALYSIS									
Villa et al 2013 Finland	RCT Meta-analysis	152 riskfactors and abnormal a.uterina Doppler	31	I=61 ASA 100mg/d 4(66.6%) C=60 placebo PE 10(16.7%) p=ns	Meta-analysis jan 1965 jan 2012 2 studier 50-150mg <16 gw i.e. 3 studies PREDO study group	+	+	?	Moderate
				RCT					

Ayala et al 2013 Spain	RCT	350 Risk pregnancy w12-w16		I1= 100 mg ASA at 8.00 58 I2= 100mg ASA at 16.00 59 I3= 100mg ASA at 22.00 59 C1, C2, C3= Placebo at 8.00, 16.00 or 22.00 59, 57, 58 I3 vs C3 p=<.001	In favour of intake at night	?	-	?	Moderate
Cantu et al 2015 USA	RCT	2539 Obese women w13-26	36	I1= 225, 60mg ASA <w16 I2= 1029, 60 mg ASA ≥w16 I3=756, 60 mg ASA BMI <30 I4=487, 60mg ASA, BMI ≥30 C1=236 Placebo <w16 C2= 1013 Placebo ≥w16 C3= 756 Placebo, BMI <30 C4= 480 Placebo, BMI ≥30 p=ns	Secondary analysis of earlier study, limited power. Outcome PE	-	-	-	Low
Caritis S et al 1998 USA	RCT MC	2539	36	I=60mg ASA1254 C=Placebo 1249 RR 0.9 95%CI 0.8-1.1	2539 Risk patients (IDDM, CH, Multifetal, history PE)	?	?	?	Moderate
Dixon C L et al 2017 USA	RCT	2479 461 PE		I= 60 mg ASA C=Placebo p=ns	Secondary analysis of multicenter RCT. Logistic regression analysis. Start 13-26 gw, mean 20±4 gw Outcome onset PE, time of delivery				
Groom et al 2017 New Zealand, Australia, Netherlands	RCT	160	11	I= Enoxaparin 40 mg(4000 IU) and ASA 100 mg (72) C= Standard Care (ASA 100 mg (77) p=ns	Riskpopulation, 6gw- <16gw PE and IUGR Small population	+	+	+	High
Liu FM et al 2016 China	RCT	115	17	I= 100mg ASA n=50 C= placebo n=48 p<0.05	PE High risk patients	+	-	?	Moderate
Poon LC et al 2017 UK	RCT MC	1620		I=ASA 150 mg gw 11-13 until gw 36 (798) C=placebo (822) P=ns regarding obstric history and maternal characteristics	Sub group analysis of ASPRE Preterm PE Less effect if CHT	+	?	?	Moderate
Rolnik et al 2017	RCT	1776	156	I=150 mg 13/798 (1.6% C=Placebo 35/822 (4.5%)	Multicenter: ASPRE: UK Spain Italy Belgium Greece, Israel	+	+	?	Moderate

Multicenter				p=0.004	Start gw11-gw14 until 36 gw Outcome PE <37 gw Adverse effect ns				
Wright D et al 2017 UK	RCT MC	1620	NA	I= ASA 150 mg risk preterm PE 798 C=Placebo 822 p=0.004	PE. Secondary analysis of ASPRE study, not sufficiently powered. Start gw11-13 until gw 36 Side effects not stated	+	+	?	Moderate
Yu et al 2003 UK Brazil South Africa Chile	RCT MC	844	284	I= 150 mg ASA C= placebo O=PE p=0.06 ns	Risk for PE abnormal a.uterine doppler at 23 gw Late inclusion	+	?	+	Moderate
PROSPECTIVE/RETROSPECTIVE COHORT RETROSPECTIVE CASE CONTROL									
Navaratman et al 2018 UK	Prospective cohort	180	24	I= 75 mg ASA High risk for PE	Aspirin non-responsiveness Longitudinally showed no consistent non-responsiveness Urine metabolites	-	-	+	Low
Park et al et al 2015 Australia	Retrospective cohort	5.783 I=2.717 C=3.066		I= 36 (1.32%) PE and of these 1 (0.04% early PE <w34, 150 mg ASA at night C=71(2.36%) PE and of these 12 (0.4% early PE) p=0.01	FMF early PE algorithm Observation only PE 1.42 % vs 2.36%, low incidence Historical controlgroup	+	-	?	Low
Stott D et al 2017 UK	Case-control	136 vs 300		I=Risk for PE 136 C=Low risk 300 NA	Hemodynamic profile in early pregnancy in relation to PE and IUGR PVR and MAP increased in risk groups. CO reduced in the group with PE and IUGR (22)				Low
Lan et al 2018 Australia, Denmark	Retrospective case control	4.978 eligible 113 late PE		I=150 mg ASA at night, gw 11-13+6 until gw 36, (40 high risk patients for early and severe PE) C= no ASA, (73 low risk patients) O=Late onset PE ≥34 gw p= ns	Two different populations compared. Risk evaluation according to FMF. All developed late PE	-	-	-	Low

Tolcher et al 2017 USA	Retrospective nested cohort	17.256 417 history of PE		I=PE before 2014 C=PE after 2014 aRR 0.70;95% CI, 0.52-0.95	Impact of USPSTF recom aspirin Recurrent PE decreased 30% I e all high risk patients. Doses not reported				Low

5. Övrig profylax

Treatment of preeclampsia/eclampsia Literature search 160225 and 180130
Prophylaxis preeclampsia
Outcome variable: Efficacy: Ca Vit D, Folic acid, exercise…

Author, Year, Country	Study design	Number of studies/ patients	With-drawals - dropouts	Results	Comments	Problems			Quality
Calcium/ Vitamin D supplementation									
An et al 2015 China	SR	4/ 14.564	NA	I=Ca >1g/d from w11 16 %reduction GH C=Placebo ns regarding preeclampsia	757 studies initially	+	+	?	Moderat
Arain et al 2015 UK	SR	7/ 26.924		I=VitD supplementation (0.5 µg/3d, 5-20 µg/d , 542 IU) C=0 Positive association of vitamin D deficiency with PE	8.283 studies initially, 1 RCT, 3 cohort, 3 nested control	+	+	-	Moderat
Khaing et al 2017 Thailand, Australia	SR Meta-analysis	27 studies/ 28.000		I1= Calcium D I2= Vitamin D I3=Calcium and Vitamin D C=Placebo/standard supplementation/no supplementation Pooled effect 0.54(95% CI:0.41, 0.70), 0.47(95%CI:0.24, 0.89) 0.50(95%CI:0.32, 0.78) i.e reduced risk 46%, 53%and 50% respectively	PE, PIH	+	+	+	High
Purswani et al 2017 USA	SR Meta-analysis	33 studies 22.057		I=Vit D 15-20ug/d supplementation C=Vit D <5ug/d O=PE p= ns	2 RCT, otherwise cohort or cross-sectional	+	+	+	High
Roth D E et al 2017 Canada	SR	43 studies/ 8.406		I=Vit D >600 IE/d C=placebo /no vitamin D / vitamin D≤600 IU/d p= ns	Only 8 studies had low risk of bias	+	+	?	Moderat
Tang et al 2014 Australia	SR Meta-analysis	10/ 24.787	NA	I=Ca++ suppl 1.5-2 g/d C=Placebo (RR 0.93, 95% CI 0.83-1.04)	Some evidence for calcium supplementation but possibility of	?	+	+	Moderat

				(RR 0.32 95% CI, 0.21-0.49)	publication bias and a lack of large trials				
Omega 3/ Fish oil									
Chen et al 2015 China	SR RCT	11/ >5000 participants	NA	I=Fish oil second trimester (200-4.950 mg/d) C=soya, oliv,egg p=ns	702 studies included initially Outcome GDM, PIH, PE.No difference low – high risk pregnancies. Other advantages?	+	?	+	Moderat
Saccone et al 2016 Italy	SR	34/ 14.106 single, 2.578 Duplex		I= Omega 3 ((100-1080 mg/d DHA (docosahexaenoic acid) 140-3.00 mg/d EPA (epaeicosapentaenoic acid)) C= placebo p=ns	7 studies (2.869 singleton pregnancies) evaluated prevention of PE, IUGR Other studies evaluated GD, Preterm birth, PM, SGA)	+	+	+	High
Folic acid supplementation/B6/MTHF									
Hua X et al 2016 Canada/China	SR Meta-analysis	13 studies		I=Folic acid supplementation 0.1 – 5 mg/pre and postconsept C= non supplementation p=ns	PE	?	?	+	Moderat
Salam et al 2016 Canada, Pakistan	SR	4/ 1.646		I=B6 Pyridoxine 1.9-25 mg/d and 100 mg/d C= Placebo Ns	Low quality of evidence regarding PE	+	+	+	High
Shim S-M et al 2016 Korea	Meta-analysis	21 studies/ 201.661	15 studies	I=Multivatamin with folic acid 0.4 mg I=folic acid supplementation 0.4 – 1.0 mg C=Placebo p = ns	6 studies PRISMA	+	+	+	High

Martinussen et al 2015 Ireland	Prospective cohort	9.576 invited	5.929	I=Folic acid >200 ug/d C= non supplementation OR 0.6(95%CI 0.4-1.0)	PE SGA Riskreduction PE in lean women (BMI<25)	?	-	-	Low
Wen SW et al 2016 Canada	Prospective cohort	8.085	316	I= Folic acid supplementation ≥1.0mg(7.265) C=no folic acid (404) O=P aOR 0.37 95%CI 0.18-0.75 only in high risk women	95% had folic acid supplementation lab analysis only in selected group of 902 women between 2006-2008.	+	-	-	Low
De Ocampo MPG et al 2017 USA	Retrospective cohort	3.247		I=Folic acid supplementation before pregnancy I=Folic acid supplementation at pregnancy C=Non users P=.003	PE Doses not stated	+	-	-	Low
Saccone et al 2016 Italy	Retrospective cohort	303 History of PE		I= 5MTHF 15 mg= 157 PE 21.7% C= Non 5MTHF=146 PE 39.7% p=0.019	All participants recieved aspirin 100mg/d	+	-	-	Low
L-Arginine/LMH									
Dorniak-Wall et al 2014 Australia	SR	7/884 patients		I=L-arginine 14-40 g/d oral or i.v. C=Placebo Riskreduction in PE in women at risk (RR 0.34, CI 95%, 0.21-0.55)	Riskreduction in patients at risk also in women with hypertensive disease	+	?	+	Moderat
Mastrolia et al 2016 Italy, Israel	SR Meta-analysis	5/797		I=LMH (Enoxaparin 20 mg/4000 IU or Dalteparin 5000 IU or adjusted to maternal weight) C=Placebo/no treatment PE (RR 0.366; 95% CI, 0.219-0.614) P=0.002	PE Abruption, FGR, FD PRISMA Few studies included	+	+	+	High
Rodger M et al 2014 Canada	SR	6 854		I= LMH (Dalteparin 5000 IU +/- ASA, Nadroparin 3800 IU, Enoxaparin 4000 IU +/- ASA C=ASA or no treatment RR reduction 0.52 95%CI 0.32-0.86	6 studies of risk patients Composite measure, high heterogeneity	+	+	+	High
Rodger et al 2016 Canada	SR Meta-analysis	8/(963) 877 riskpatients		I=LMH different types and doses (480) C= aspirin/ no treaatment (483) p=ns	Placentamediated complications PRISMA	+	+	+	High

Haddad B et al 2016 France	RCT Open label MC	257	8	I=Enoxaparin 4000 IU and 100mg ASA (124) C=100 mg ASA (125) p=ns	History of severe PE < 34 gw Outcome Placentamediated pregnancy complications	+	+	+	High
Physical Activity/diet									
Allen et al 2014 UK	SR Meta-analysis	18/ 8.712		I1= Diet I2= Diet, physical activity, life-style I3= Essential fatty acid supplementation C= non intervention RR 0.81 p=0.006	PRISMA	+	+	+	High
Aune et al 2014 Norway	SR	15 studies	NA	I= Physical activity before and in early pregnancy C= no activity RR 0.79 (0.70-0.91)	PE Non linear relation of activity before, but linear correlation in early pregnancy. Different kinds of quantative activity	+	?	-	Low
Magro Malosso 2017 Italy, USA	SR Meta-analysis	17 studies 5.075		I=Aerobic exercise 30-60 min 2-7 times weekly C=No excercise session PE 5.9% vs 8.5%; RR 0.70, 95%CI 0.53-0.83) GH 2.5% vs 4.6%: RR 0.54, 95%CI 0.40-0.74)	GIH, PE 7 studies included in the meta-analysis PRISMA	+	?	+	Moderat

6. Antihypertensiva, maternell effekt

<table>
<tr><td colspan="7">Systematic reviews and meta-analysis n=10
Treatment of hypertension with antihypertensive therapy and/or intervention, Hypertension: mild to moderate or severe, chronic hypertension, gestational hypertension, or preeclampsia/eclampsia), antepartum n=32
Outcome variable: Antihypertensive therapy: Efficacy and maternal mortality and maternal short term outcomes. Interventionist care (delivery) vs expectant care maternal mortality and maternal short term outcomes. Corticosteroids for fetal lung maturation: maternal outcomes n=43 articles included</td></tr>
<tr><td rowspan="2">Author, year, country</td><td rowspan="2">Study design</td><td rowspan="2">Number of studies/ patients</td><td rowspan="2">With drawals - dropouts</td><td colspan="2">Results</td><td rowspan="2">Comments</td><td rowspan="2">Quality (High Medium Low)</td></tr>
<tr><td>Intervention</td><td>Control</td></tr>
<tr><td rowspan="10">Abalos, 2014 Cochrane</td><td rowspan="10">SR</td><td rowspan="10">49 RCTs,
Totally 4723 women with mild to moderate hypertension
C1=29 trials, 3350 women
C2=22 trials, 1723 women</td><td rowspan="10"></td><td>I: Antihypertensive therapy (betablockers, metyldopa, calcumblockers either alone or in combination with other drugs):</td><td>C:1 placebo or no treatment</td><td rowspan="10">Secondary other outcomes were:
Severe preeclampsia 0.54 (0.24-1.23)
Cesarean section 0.92 (0.83-1.02)
Also comparisons by type of hypertension at trial entry, by gestation at trial entry and by use of placebo.</td><td rowspan="10">High</td></tr>
<tr><td colspan="2">Severe hypertension
(sBP≥170 mmHg and/or dBP ≥110 mgHg)
:</td></tr>
<tr><td>125/1336</td><td>242/1222
RR 0.49 (95% CI 0.40-0.60)</td></tr>
<tr><td colspan="2">Proteinuria/preeclampsia</td></tr>
<tr><td>251/1476</td><td>255/1375
RR 0.93 (95% CI 0.80-1.08</td></tr>
<tr><td colspan="2">Maternal mortality</td></tr>
<tr><td>2/289</td><td>1/236
RR 1.08 (0.24-4.83)</td></tr>
<tr><td colspan="2">Eclampsia</td></tr>
<tr><td>0/298</td><td>1/280</td></tr>
</table>

					RR 0.34 (0.01-8.15)		
				HELLP			
				4/98	2/99 RR 2.02 (0.38-10.78)		
				Pulmonary oedema			
				4/185	2/140 RR1.24 (0.30-5.12)		
				I: Antihypertensive therapy (any, betablockers or calcumblockers	C:2 Metyldopa		
				Severe hypertension			
				C2 Any hypertensive C2:1 Beta blocker C2:2 Calcium channel blocker	C2 Metyldopa 0.54 (0.30-0.95) C2:1 Metyldopa 0.59 (0.33-1.05) C2:2 Metyldopa 0.23 (0.04-1.22)		
				Proteinuria/preeclampsia			
				C2 Any hypertensive C2:1 Beta blocker C2:2 Calcium channel blockers	C2 Metyldopa 0.73 (0.54-0.99) C2:1 Metyldopa 0.75 (0.53-1.05) C2:2 Metyldopa 0.66 (0.34-1.27)		
				I: Antihypertensive therapy (any, glyceryl trinitrate or betablockers	C:3 (Calcium channel blockers)		

				Severe hypertension			
				C3 Anyhypertensive C3:1 Glyceryl trinitrate C3:2 Beta blockers	C3 Calcium channel blockers 2.09 (0.96-4.57) C3:1 calcium channel blockers 1.56 (0.07-35.67) C3:2 calcium channel blockers 2.14 (0.96-4.80		
				Proteinuria/preeclampsia			
				C3 Any hypertensive C3:1 Glyceryl trinitrate C3:2 Beta blockers	C3 Calcium channel blockers 2.15 (0.73-6.38) C3:1 Calcium channel blockers 1.0 (0.10-9.96) C3:2 Calcium channel blockers 2.67 (0.75-9.42)		
Churchill et al, 2013 Cochrane	SR	4 RCTs 425 women		HELLP		Interventionist care was: either induction of labour or caesarean section after corticosteroids to improve fetal lung maturation, (in practice after 24 to 48 hours). Expectant care was: corticosteroids, stabilization of the woman's condition and then, aim to delay delivery. There were insufficient data to draw any conclusions about the effect a policy of expectant care had on the mother's health. None of the studies included	High
				Interventionist 1/46	Expectancy 2/49 RR 0.53 (0.05-5.68)		
				There were no maternal deaths, eclampsia, stroke, pulmonary oedema reported			
				Cesarean section			
				Interventionist 201/222	Expectancy 107/203 RR 1.09 (1.01-1.18)		

						had sufficient sample size to demonstrate differences in maternal outcome. Cesarean section was secondary outcome. No other significant differences for other secondary maternal outcomes.	
Cluver et al, 2017, Cochrane	SR	5 RCTs, 1891 women		Composite maternal morbidity and mortality: There was a lower risk of composite maternal mortality and severe morbidity for women randomised to receive planned early delivery (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.57 to 0.83, two studies, 1459 women (evidence graded high)). There were no clear differences between subgroups based on our subgroup analysis by gestational age, gestational week or condition. Planned early delivery was associated with lower risk of HELLP syndrome (RR 0.40, 95% CI 0.17 to 0.93, 1628 women; three studies) and severe renal impairment (RR 0.36, 95% CI 0.14 to 0.92, 100 women, one study). There was no clear difference between groups for caesarean section (RR 0.91, 95% CI 0.78 to 1.07, 1728 women, four studies, evidence graded moderate), or in the duration of hospital stay for the mother after delivery of the baby (mean difference (MD) -0.16 days, 95% CI -0.46 to 0.15, two studies, 925 women, evidence graded moderate)			High
				Interventionist	Expectancy		
Crowther Cochrane. 2015	SR	10 RCTs 4733 women		Chorioamnionitis		Women considered to be at risk of preterm birth who had received a single course of prenatal corticosteroid seven or more days previously were included.	High
				Repeat doses of betamethasone 140/2152	Single dose of betamethasone 118/2109		

					RR 0.1.16 (0.92-1.46)	Secondary maternal outcomes included death, hemorrhage, mode of delivery, pyrexia etc. there was no maternal death. No statistically significant differences were seen between treatment groups, for the following outcomes: risk of prelabour rupture of the membranes after trial entry, hypertension, mode of birth, postpartum haemorrhage or postnatal pyrexia. More side effects were reported in some studies in repeated doses group (insomnia, bruising at injection site).	
				Puerperal sepsis			
				Repeat doses of betamethasone 72/1525	Single dose of betamethasone 61/1526 RR 1.15 (0.83-1.60)		
Duley, 2013 Cochrane	SR	35 RCTs. Totally 3573women with very high blood pressure, sBP ≥170 or dBP ≥105 mm Hg		**Labetalol versus hydralazine**		Eleven more comparisons. Persistent high BP was more common with hydralazine than with calcium channel blockers. "The choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug; on what is known about adverse effects; and on women's preferences. Exceptions are nimodipine, magnesium sulphate (although this is indicated for women who require an anticonvulsant for prevention or treatment of eclampsia), diazoxide and ketanserin, which are probably best avoided."	High
				Maternal death			
				0/100	0/100		
				Eclampsia			
				0/110	0/110		
				Persistent high blood pressure			
				11/110	7/110 RR 1.57 (0.66-3.74)		
				Labetalol versus calcium channel blockers:			
				Eclampsia			
				1/35	2/35 RR 0.72 (0.05-10.26)		
				Persistent high blood pressure			

				16/55	14/55 RR 1.14 (0.62-2.09)	Primary outcomes were maternal death, eclampsia, stroke, persistent high blood pressure. Secondary outcomes included any of serious maternal morbidity defined as, stroke, kidney failure, liver failure, HELLP syndrom, disseminated intravascular coagulation, pulmonary oedema, kidney failure, liver failure, HELLP, DIC, pulmonary oedema, hypotension, side effects of the drug, abruption of the placenta or antepartum haemorrhage, need for magnesium sulphate, elective delivery: induction of labour or caesarean section, caesarean section: emergency and elective, postpartum haemorrhage: defined as blood loss of 500 mL, use of hospital resources: visit to day care unit, antenatal hospital admission, intensive care (admission to intensive care unit, length of stay) ventilation, dialysis, postnatal depression, breastfeeding, at discharge and up to one year after the birth, women's experiences and views of the interventions childbirth experience, physical and psychological trauma, mother-infant interaction and attachment.	
				Labetalol versus metyldopa			
				Persistent high blood pressure			
				20/38	15/34 RR 1.19 (0.74-1.94)		
				Calcium channel blockers versus hydralazine			
				Persistent high blood pressure			
				13/160	34/153 RR 0.38 (0.21-0.70)		

Firoz, 2014, Canada	SR	16 RCTs, 15 during pregnancy (914 women) and one postpartum (38 women) with very high BP (sBP ≥160 mmHg and/or dBP ≥110 mmHg		Single oral antihypertensive agents: C1Oral/sublingual nifedipine C2 Nifedipine capsules C3 Oral labetalol	C1:1Parental hydralazine iv C1:2Labetalol iv No difference in efficacy or maternal outcomes C2 Nifedipine tablets Higher rates of maternal hypotension with capsules C3 Oral methyldopa No difference in efficacy or maternal outcomes	Inclusion criteria was at least one arm with oral antihypertensive. Overlap with Duley? Primary outcome: effectiveness	High
Guida et al, 2017, Brazil	SR (2 RCTs and 4 cohort studies)	Women with preterm preeclampsia< 34 GW or between 34 and 37 GW N=183, 703, 670120, 696, 516 and 199, respectively		< 34 GW: Immediate delivery vs expectancy: Maternal outcomes were similar 34 – 37 GW: Immediate delivery vs expectancy: Expectant management had slightly higher rate of progression to severe maternal disease.		No pooled estimates presented	Low
Roberts, 2017 Cochrane	SR (30 RCTs)	7774 women and 8158 infants		Treatment with antenatal corticosteroids does not increase the risk of chorioamnionitis (RR 0.83, 95% CI 0.66 to 1.06) or endometritis). No increased risk in maternal death was observed.		Author conclusion: this update supports the continued use of a single course of antenatal corticosteroids to accelerate fetal lung maturation in	High

						women at risk of preterm birth. A single course of antenatal corticosteroids could be considered routine for preterm delivery.	
Shekhar, 2015, India	SR	7 RCTs, 363 women with severe hypertension		Oral nifedipine	Labetalol iv	Oral nifedipine was associated with significant reduced risk of persistent hypertension. Severe hypertension defined as sBP ≥160 mmHg and/or dBP ≥105 mmHg. Persistent hypertension defined as need for additional hypertensive drug, or failure to lower the BP to "safe" levels Serious maternal morbidity defined as stroke, placental abruption, DIC, pulmonary oedema, renal failure or need for ICU	High
				Persistent hypertension			
				6/187	15/176 RR 0.42 (0.18-0.96)		
				Serious maternal morbidity			
				6/125	8/131 RR 0.73 (0.28-1.88)		
				Maternal mortality			
				0/166	1/157 RR 0.30 (0.01-7.22)		
Wang et al 2017 Arch Gynecol Obstet, China	SR (7 RCTs)	1501 women		Maternal complications >34 v (one trial, HYPITAT)		No maternal deaths or strokes, one study reported one case of eclampsia in each group. Less increase in sBP and dBP and less need for antihypertensive therapy in intervention group	High
				88/377	138/379 RR 0.64 (0.51-0.80)		
				Maternal outcome: placental abruption <34 v			
				7/230	17/245 RR0.43 (0.19-0.98)		
Original articles n=32							
Astudillo, 2013, Spain	Retrospectiv e observationa	Women with severe PE between 23+6 and 33+6 GW: GrA: Women		Mean prolongation of pregnancy		Conclusion: Women with severe EO-PE and associated risk factors benefit from expectant management.	Low
				Gr A: mean 8.42 days (SD 7.46; range 2-29 days)	Gr B 10.5 days (SD 8.24; range 2-41 days).		

	l cohort study	with concomitant risk factors n=26) GrB: women without risk factors (n=33)		No significant difference in maternal complication (pulmonary odema, renal impairment, abruptio placentae, eclampsia etc)	Concomitant risk factors were associated medical condition, HELLP, severe oligohydramniosis, fetal growth restriction, multiple pregnancies	
Broekhuijsen , 2015, the Netherlands	Retrospective cohort study	Chronic hypertension: 3457 women Controls: 984 932 normotensive women		Adverse maternal outcome 993/3 457 vs 65 008/984 93 AOR 5.7 (5.3-6.2)	Conclusion: Optimal time for delivery for women with chronic hypertension between 38 and 40 GW. Adverse maternal outcome was a composite measure of one of more of severe hypertension, preeclampsia, eclampsia, placental abruption, postpartum hemorrhage ≥1000 ml, thromboembolic event or maternal death.	Medium
DelgadoDe Pasquale, 2013, Panama	RCT	261 women with severe hypertension (sBP≥160 mmHg/dBP ≥110 mmHg	19	Efficacy: final BP, number of antihypertensive doses Hydralazine iv (n=130): Final sBP 144 (8.3) mmHg Final dBP 91 (8.3) mmHg Final MAP 109 (6.8) mmHg Number of doses necessary for control of hypertensive crisis 1.4 (0.6) Labetaol iv (n=131): Final sBP 144 (8.2) mmHg, p=0.86 Final dBP 92 (8.3) mmHg, p=0.48 Final MAP 109 (7.2) mmHg, p=0.39 Number of doses necessary for control of hypertensive crisis 1.3 (0.6). p=0.25	Hydralazine iv vs labetalol iv: No difference in new episodes of hypertensive crisis during pregnancy or the first 24 h postpartum or adverse reactions (headache, visual symptoms, epigastric pain, palpitations, nausea, vomiting and flushing)	Low
Dhananjaya, 2015 India	RCT	Women with BP ≥160/110 mmHg, ≥28 GW	NR	Efficacy: time to achieve BP≤150/100mmHg Oral nifedipine (n=30) 14.0 (6.87) min Labetalol iv (n=30) 25.17 (12.76) min	Shorter time to target therapeutic BP with nifedipine. No difference in maternal complications (hypotension,	Low

					p=0.014	palpitation, nausea and vomiting, chest pain, headache, fetal tachycardia, HELLP, eclampsia, renal failure	
				Number of doses required to achieve target BP			
				1.87 (0.63)	2.53 (12.76) p=0.158		
Duro-Gomez et al, 2017, Spain	Retrospective cohort study	Nifedipine (N):43 crisis (10 women), Labetalol (L): 12 crisis (4 women)	NR	Mean time needed to achieve target BP (> 150/95 mm Hg): N group: 31.3 min and L group 53.5 min (p=0.03). Mean reduction in BP in N group: 31.19/15.67 mm Hg and in L group 30.1/11 mm Hg (p=0.67/0.84). Failure to achieve BP target N group in 1 case and L group in 3 cases (p=0.01). No difference in maternal adverse outcomes.		Only 14 women, but 55 crisis	Low
Durst et al, 2016, USA	Retrospective cohort study	320 women: 37+0-37+6: n=67 38+0-38+6: n=76 39+0-39+6: n=177	NR	CS (=primary outcome): 37+0-37+6: 18/67 (26.9%) 38+0-38+6: 15/76 (19.7%) 39+0-39+6: 53/177 (29.9%) p value for trend=0.39 Composite maternal outcome 37+0-37+6: 18/67 (26.9%) 38+0-38+6: 17/76 (22.4%) 39+0-39+6: 68/177 (38.4%) **p value for trend=0.03** AOR (95% CI) for maternal and neonatal outcomes compared to ≥39 GW Composite maternal: 37+0-37+6: 0.58 (0.31-1.08) 38+0-38+6: **0.45 (0.24-0.84)** Any (neonatal or maternal adverse outcome: 37+0-37+6: 0.60 (0.33-1.10) 38+0-38+6**: 0.50 (0.28-0.90)** Neonatal outcomes were similar among the groups.		Composite maternal outcome included CS, endometritis, PPH, DVT, readmission, BP treatment pp, wound infection, CA. Composite neonatal outcomes included NICU admissions, length of stay ≥5 days, Apgar score at 5 ≤3 RDS or death. Any adverse outcome was any adverse maternal or neonatal outcome Adjusted for BMI	Low
Harper et al, 2016, USA	Retrospective cohort study	Women with a live singleton pregnancy reaching ≥36 GW		Expectant management beyond 39 GW was associated with increased risk for Severe PE (1.1% vs 10.3%, p= 0.001) AOR 0.07 (95% CI 0.01-0.5)		Adjusted for baseline renal disease and aspirin use	Medium

		and chronic hypertension: All, (planned delivery vs expectant management) 36 GW n=683 (20 vs 663), 37 GW n= 572 (39 vs 533), 38 GW n= 414 (30 vs 384) and 39 GW n= 280 (124 vs 156)		Any PE 4.5% vs 18.7% AOR 0.1 (95% CI 0.04-0.35) No difference for CS in labour		
Kawakita et al, 2018, USA	Retrospective cohort study	Women with PE (mild or severe), ≥ 34 GW, singleton pregnancy IOL: n=5104 CS: n= 402	NR	Primary outcome: IOL 4.3%, planned CS 3.7% AOR 1.94 (95% CI 0.89-4.24) Maternal ICU IOL 2.4% vs1.2% AOR 3.29 (95% CI 1.02-10.64) Other maternal outcomes NS When stratified for parity NS for primary outcome and ICU admission	Stratification for parity Adjusted for age, race/ethnicity, marital status, insurance type, hospital type, diabetes (preexisting or gestational), gestational age, body mass index, and type of preeclampsia (planned cesarean delivery as referent).	Medium
Madazli, 2013, Turkey	Cohort study	144 women, (early onset preeclampsia [EO-PE]=91 [45 mild and 46 severe] and late onset preeclampsia [LO-PE]=63 [34 mild and 29 severe])	NR	Maternal complications Mild preeclampsia EO-PE: No / LO-PE: No Maternal complications Severe preeclampsia EO-PE: 18 (39.1) / LO-PE: 12 (41.3) NS between EO-PE and LO-PE	Maternal complications occurred only in severe preeclampsia and at similar rates in EO-PE and LO-PE. EO-PE was defined as onset before 34+0 GW, LO-PE as onset at ≥34+0 GW. Maternal complications were sustained severe hypertension, any evidence of organ dysfunction, HELLP or admittance to ICU.	Low
Magee, 2015	RCT		49	Serious maternal outcomes		High

International study (CHIPS trial)		1030 women with nonprotein-uric preexisting or gestational hypertension		Less-tight control 18/493	Tight control 10/488 AOR 1.74 (0.79-3.84)	Maternal outcomes were secondary outcomes. Primary outcome was a composite of pregnancy loss (table XX= barnutfallstabellen). Serious maternal outcomes were death, eclampsia, uncontrolled hypertension, TIA or stroke, pulmonary edema, renal failure, transfusion. Adjusted for type of hypertension (preexisting vs gestational), center, use of antihypertensive therapy at randomization, previous BP of 160/110 mmHg or higher during the pregnancy, gestational diabetes, gestational age at randomisation	
				Preeclampsia			
				Less-tight control 24/493	Tight control 223/488 AOR 1.14 (0.88-1.47)		
				Severe hypertension			
				Less-tight control 200/493 (40.6%)	Tight control 134/488 (25.5%) AOR 1.80 (1.34-2.38)		
Magee, 2016a International study (CHIPS trial), BJOG	Cohort study.Secon-dary analysis of CHIPS trial (RCT)	481/987 CHIPS recruits at randomisati and 657/987 CHIPS recrutis postrandomisation		At randomization Metyldopa vs Labetalol		Women treated with metyldopa versus labetalol (particularly those with pre-existing hypertension) may have better outcomes. Adjusted for allocation group, type of hypertension (preexisting vs gestational), center, use of antihypertensive therapy at randomization, previous BP of 160/110 mmHg or higher during the pregnancy, gestational age at randomization and for the postrandomisation analysis	Moderate
				Severe hypertension			
				79/241	80/237 AOR 0.80 (0.48-1.34)		
				Preeclampsia			
				113/241	104/236 AOR 1.12 (0.78-1.61)		
				Post- randomization before delivery Metyldopa vs Labetalol			
				Severe hypertension			
				54/224	162/433 AOR 0.51 (0.31-0.83)		

				Preeclampsia		whether women were on antihypertensive at randomization (yes/no)	
				89/224	225/431 AOR 0.55 (0.36-0.85)		
Magee, 2016b International study (CHIPS trial) BJOG	Cohort study.Secon-dary analysis (RCT)	566/987 CHIPS recruits at randomisation and 815 /987 CHIPS recruits postrandomisation		At randomization Less-tight vs tight. Metyldopa (MD) and labetalol (LB)		Outcomes for "less-tight" versus "tight" control were not dependent on use of metyldopa or labetalol. Adjusted for type of hypertension (preexisting vs gestational), center, use of antihypertensive therapy at randomization, previous BP of 160/110 mmHg or higher during the pregnancy, gestational age at randomization and for the postrandomisation analysis whether women were on antihypertensive at randomization (yes/no)	Moderate
				Severe hypertension			
				LB 45/110 MD 48/125	LB 35/127 AOR 1.67 (0.92-3.02) MD 30/116 1.82 (1.01-3.28)		
				Preeclampsia			
				LB 53/109 MD 58/125	LB 51/127 AOR 1.46 (0.84-2.52) MD 55/116 AOR 0.97 (0.57-1.65)		
				Post- randomization before delivery Less-tight vs tight			
				Severe hypertension			
				LB 91/186 MD 33/98	LB 71/247 AOR 1.43 (1.58-3.74) MD 21/126 AOR 2.65 (1.36-5.18)		
				Preeclampsia			
				LB 106/184 MD 39/98	LB 119/247 AOR 1.48 (0.98-2.23) MD 50/126 AOR 1.10 (0.62-2.40)		
Magee et al, 2016 Hypertension	Cohort study.Secon-dary analysis (RCT)	1030 women with nonprotein-uric preexisting or gestational hypertension		334 (33.9% of the women in the CHIPS trial developed severe hypertension (sBP≥160 mm Hg or dBP ≥110 mm Hg), which was associated with the primary outcome (pregnancy loss or high level neonatal care > 48 hours), birth weight < 10^{th} percentile, preeclampsia, PTD,			Moderate

				elevated liver enzymes (p<0.001), low platelets (p=0.006), prolonged hospital stay (p=0.03). The association with severe hypertension and severe maternal complications was seen only in the less tight group 13/200 (severe hypertension) vs 5/293 (no severe hypertension)(p=0.02) and not in the tight group (3/124 versus 7 /354) (p=0.93)		
Magee et al, 2016 International study (CHIPS trial) AOGS	Cohort study.Secon-dary analysis (RCT)	1030 women with nonprotein-uric preexisting or gestational hypertension		19 candidate predictors collected at randomization were evaluated for prediction on the probability of adverse outcome, Included treatment group ; "less tight" and "tight control" etc. AUC ≥ 0.70 was considered as a potentially useful model Conclusion was that maternal and current pregnancy clinical characteristics cannot predict adverse outcome in the index pregnancy		Moderate
McKinney et al, 2016, AJOG, USA	Retrospectiv e single center cohort study	60 women with PE and FGR and 139 with PE and no FGR		Interval do delivery (from diagnosis of PE) No FGR GA at delivery, 33 (30-34) wks Interval do delivery, median (IQR) 5 (2-12) days FGR GA at delivery, 29 (26-32) wks p<0.001 Interval do delivery, median (IQR) 3 (1-6) days p<0.001 Latency <7 days AOR 1.66 (1.12-2.47 Indications for delivery No FGR Severe PE 58.8% Neurological symtoms 37.5% FGR Severe PE 48.3% p=0.17 Neurological symtoms 16.7% p=0.003	FGR was associated with a shorter interval to delivery Onset of PE was < 34 GW Adjustment: maternal race, smoking, chronic hypertension, GA at delivery, severe PE, fetal sex	Low

				HELLP 15.4%	HELLP 13.3% p=0.70		
Nooij, 2014 The Netherlands	Retrospective nested case control study and meta-analysis (2 RCTs)	Labetalol 76, nicardipine 99		Efficacy: lowering the BP without adding another drug		Success rate higher for nicardipine. Nicardipine associated with more tachycardia. No difference in maternal headache or sudden hypotension (neither the Dutch study nor the MA of the two studies)	Low
				Labetalol 64/76 MA (2 RCTs) 83/106	Nicardipine 96/99 RR 1.15 (1.04-1.28) MA (2 RCTs) 117/129 RR 1.14 (1.02-1.28)		
				Side effect (maternal tachycardia)			
				Labetalol 1/76 MA (2RCTs) 1/106	Nicardipine 7/99 RR 5.37 (0.68-42.75) MA (2 RCTs) 10/129 RR 5.87 (1.09-31.75)		
Owens et al, 2014 Journal of the Mississippi Med Assoc	RCT	Immediate delivery: n=94 Expectancy: n=75	3 and 11	Immediate delivery (within 12 hours)	Immediate vs Expectancy Progression to severe PE 3% (3/94) vs 41% (31/75) P=0.0001	Study stopped at 183/ 220 patients	Low
Patel et al, 2017, India, The J Ob Gyn India	RCT	I= 76 (hydralazine) C=76 (labetalol)	No	Number of drug doses to achieve target BP, One dose/ Two doses		Not blinded	Low
				Hydralazine 53/76 (69.7%) 23/76 (30.3%)	Labetalol 62/76 (81.5%) 12/76 (15.8%) p=0.04		
				Time to achieve target BP			
				26.32 (9.78) min	12.63 (7.19) min p<0.0001		
				Maternal outcomes and side effects were similar			

Roland et al, 2017, USA, J Pernatol	Retrospective cohort study	IOL: 25 773 women with PE No IOL: 24 147 women with PE		Vaginal delivery at preterm (66% at 23–36 weeks) and term GAs (72%). Factors most strongly associated with successful labor induction were prior vaginal delivery (aOR, 5.91; 95% CI, 5.44–6.43) and young maternal age (aOR 1.44; 95%CI, 1.30–1.59). Factors negatively associated with vaginal delivery after labor induction for PE included black race, birth weight >4000 g or <2500 grams, maternal obesity, prior cesarean, fetal malpresentation and abnormal pregnancy weight gain. Increasing GA was only modestly associated with higher odds of vaginal birth (aOR 1.03; 95%CI 1.01–1.05)		Medium
Sabir et al, 2016, Paksitan, J Postgrad Med Inst	Quasi RCT	I=50 nifedipine, C=50 hydralazine		Number of drug doses to achieve target BP Mean (SD) Hydralazin 2.74 (1.35) / Nifedipine 3.86 (1.45) P<0.001 Time to achieve target BP Hydralazin 41.10 (20.29) min / Nifedipine 57.90 (21.86) min P<0.001	Not blinded	Low
				Maternal side effects were similar		
Schoen et al, 2017, USA and Italy, J Mat Fetal Med	Retrospective cohort study	365 singleton pregnancies with superimposed PE, 198 outpatients and 167 inpatients	No	Similar rate of maternal morbidity (any of severe features at delivery, eclampsia, HELLP; ICU, abruption, PPH, maternal death) in outpatients compared to those managed as inpatients (36.4% versus 41.3%, aOR 0.82, 95%CI 0.55–1.17)	Adjusted for age, BMI, parity, smoking, ethnicity, antihypertensive drug use, concomitant diseases	Medium
Sharma et al, 2017, India, AJOG	RCT	I=30 hydralzine C=30 nifedipine	No	Time to achieve target BP Median (interquartile interval) Hydralazine 40 (5) min / Nifedipine 40 (40) min p=0.809 Number of drug doses to achieve target BP Median (interquartile interval)	Conclusion was that the effect of iv hydralazine and oral nifedipine was similar	High

				Hydralazine 2 (1)	Nifedipine 2 (2) p=0.625		
				Maternal side effects: Maternal vomiting was more common in the hydralazine group (9/30 vs 2/30 p= 0.042), other maternal outcomes were similar			
				Labetalol 3/30 (10%)	Hydralazine 7/69 (11%)		
				No woman hade sBP < 90 mm Hg or ≥30% reduction in dBP			
Sharma et al, 2017, USA Hypertension Pregnancy	RCT	I=25 labetalol C=25 nifedipine	Two	Time to achieve BP control		Not blinded	Medium
				Labetol 37.6 (32.5) h	Nifedipine 38.2 (27.6) h p=0.51		
				Labetalol achieved BP control more often with the starting dose than nifedipine and with fewer side effects. No other differences in secondary outcomes			
Shi, 2016, China, J Clin Pharm and Therapeutics	RCT	Labetalol n=73 Nifedipine n=74	No	Time to achieve BP control		Not blinded	Medium
				Labetalol 42 (28.5-68.4) min	Nifedipine 35 (24.5-71.3) min p=0.37		
				Time interval to new hypertensive crisis			
				Labetalol 3.1 (1-8) h	Nifedipine 3.4 (1-8) min p=0.58		
				No other differences in other outcomes			
Shields et al, 2017, USA, AJOG	Prospective quality improvement project	23 hospitals, 2034 with indication for treatment with iv		Compliance with utilization of iv BP medication increased by 33.2%, from a baseline of 57.1-90.3% (P < .01) during the last 6 months of monitoring. Compliance with utilization of magnesium sulfate increased by 10.8%, from a baseline of 85.4-96.2% (P <			Medium

		Mg and antihypertensives		.01). The incidence of eclampsia declined by 42.6% (1.15 ± 0.15/1000 to 0.62 ± 0.09/1000 births). Severe maternal morbidity decreased by 16.7% from 2.4 ± 0.10% to 2.0 ± 0.15% (P < .01).		
Stott et al, 2017, UK, UOGS	Cohort study	52 women with hypertension not on antihypertensive were given individualized therapy (labetalol n=40 or vasodilator n= 12) after hemodynamic monitoring		Serial hemodynamic monitoring to guide treatment compared with universal treatment reduced the rate of severe hypertension from 18% to 3.8%. Fetal growth restriction was similar despite a higher risk profile in the monitored group and longer treatment. Monitoring could identify high resistance, low-output hypertensive pregnancies with risk for fetal growth restriction.	Needs external validation	Medium
Tariq et al, 2017, Pakistan, PJMHS	RCT	Hydralazine n=50 Labetalol n=50		Maternal hypotension: 45/100 had hypotension, 35 (77.8%) in hydralazine and 10 (22.2%) in labetalol group, p< 0.05	Hypertension and hypotension no defined. Randomisation unclear (lottery). Not blinded.	Low
Van Oostward et al, 2017 The Netherlands, BJOG	Case series	n=133		Maternal complications occurred frequently (54%). Deterioration of HELLP during expectant care occurred in 48%, after 4 days. Median prolongation was 5 days (range: 0–25 days). PE in next pregnancy was 31% at mean GW 32+6	Counselling important! Better prognosis in next pregnancy	Low
Wang et al, 2017. China, J Clin Hypertension	RCT	Labetalol n=72 Nifedipine n=71		BP after 1 and 4 hours, mm Hg, mean (SD) Labetalol: 1h sBP 160.2 (14.6); 1 h d BP 102.7 (12.7); 4 h sBP 151.1 (16.1); 4 h dBP 98.6 (11.7) Nifedipine: 1h sBP 162.1 (17.2); 1 h d BP 101.6 (15.4); 4 h sBP 150.6 (18.5); 4 h dBP 97.4 (11.8) All p values >0.05 No short term adverse effects: nifedipine vs labetalol 65/71 vs 58/72 RR 1.07 (95% CI 0.92-1.24) Recovery: nifedipine vs labetalol 65/71 vs 67/72	Randomisation not presented. Placebo controlled, blinded, no demographics presented.	Medium

				RR 0.98 (95% CI 0.90-1.07)		
Webster et al, 2017, UK, Hypertension	RCT	Labetalol n=56 Nifedipine n=58	2	Labetalol vs nifedipine Mean BP 134/84 vs 134/85 mm Hg (mean difference sBP and dBP NS) Superimposed PE 8 (15%) vs 15 (26%) adj RR 1.78 (95% CI 0.74 -3.77) NS difference in gestation at delivery Nifedipine associated with a 7.4 mm Hg reduction in central aortic pressure (mechanistic outcome) White women (but not black) had a significant treatment effect by a mean 4 mm Hg (-6.6 to -0.8 mm Hg) reduction in dBP with labetalol compared with nifedipine	No blinded Not power for analysis of most adverse maternal outcomes Feasibility confirmed Conclusions were that both labetalol and nifedipine control mean BP to target in women with CHT	Medium
Zhu et al, 2017, China, Int J Clin Exp Med	RCT	I: labetalol + Mg n= 60, C: nifedipine + Mg n=60	No	BP (mm Hg) 1 hour and 4 hours after treatment Labetalol + Mg 1h sBP 142 .25 (6.58)* 1 h dBP 88.02 (2.93) 4 h sBP 134.96 (4.62)* 4 h dBP 83.85 (2.01)* Nifedipine + Mg 1h sBP 149.96 (7.35)* 1 h dBP 88.37 (3.08) 4 h sBP 140.35 (4.96)* 4 h dBP 87.58 (2.83)* *p< 0.05 Gestational age at delivery shorter in labetalol group, but PTB rate higher (?), urinary protein lower and creatinine level lower in labetalol group vs nifedipine group. More PPH in nifedipine group	Randomisation unclear, not blinded, gestational age at delivery unclear	Low
Zwertbroek et al, 2017, The Netherlands, AOGS	Retrospective analysis of a RCT (HYPITAT II) Prediction model	n=115 (22.2%) developed severe HDP, n=404 developed no severe HDP indicating delivery	No	The prediction model included: maternal age (odds ratio 0.92 per year), gestational age (odds ratio 0.87 per week), systolic blood pressure (odds ratio 1.05 per mmHg), the presence of chronic hypertension (odds ratio 2.4), platelet count (odds ratio 0.996), creatinine (odds ratio 1.02) and lactate dehydrogenase (odds ratio 1.003). The model showed good fit (p = 0.64), fair	External validity needed	Low

				discrimination (area under the curve 0.76, 95% confidence interval 0.73–0.81, p < 0.001) and could stratify women in three risk groups of average, intermediate and high risk (predicted probabilities <0.22, <0.44 and >0.45, respectively).		

7. Antihypertensiva, neonatal effekt

Systematic reviews and meta-analysis n=10
Treatment of hypertension with antihypertensive therapy and/or intervention, Hypertension: mild to moderate or severe, chronic hypertension, gestational hypertension, or preeclampsia/eclampsia), antepartum or postpartum n=41
Outcome variable: Antihypertensive therapy: Efficacy and child outcomes. Interventionist care (delivery) vs expectant care: child outcomes. Corticosteroids for fetal lung maturation: child outcomes

Author, year, country	Study design	Number of studies/ patients	With drawals - dropout s	Results		Comments	Quality (High Medium Low)
				Intervention	Control		
Abalos, 2014 Cochrane	SR	49 RCTs, Totally 4723 women with mild to moderate hypertension C1=29 trials, 3350 women C2=22 trials, 1723 women		I: Antihypertensive therapy (betablockers, methyldopa, calciumblockers either alone or in combination with other drugs):	C:1 placebo or no treatment	Also comparisons by type of hypertension at trial entry, by gestation at trial entry and by use of placebo. There were no clear differences in other secondary outcomes either including: Apgar score< 4 at 5 min,. Severe prematurity <32 and <34 wks. Admission to neonatal or intensive care nursery. Respiratory distress syndrome. Other morbidity possibly related to maternal drug therapy, such as hypo- or hypertension, hypoglycaemia and bradycardia (with beta blockers).	High
				Any fetal, perinatal or neonatal death			
				2/1682	1/1548 RR 0.71 (0.49-1.02)		
				Miscarriage			
				6/573	17/485 RR 0.39 (0.17-0.93)		
				Stillbirth			
				18/1274	11/1206 RR 1.14 (0.60-2.17)		
				Perinatal death			
				30/1243	31/1139 RR 0.96 (0.60-1.54)		
				Neonatal death			

				1/271	2/286 RR 0.79 (0.14-4.34)		
				Preterm birth <37 GW			
				289/1135	279/1006 RR 0.96 (0.85-1.19)		
				SGA			
				185/1360	165/1226 RR 0.97 (0.80-1.17)		
				I: Antihypertensive therapy (any, betablockers or calcumblockers	C:2 Methyldopa		
				Any fetal/neonatal death incl miscarriage			
				C2 Any hypertensive C2:1 Beta blockers C2:2 Calcium channel blocker	C2 Methyldopa RR 0.73 (0.42-1.27) C2:1 Methyldopa RR 0.73 (0.40-1.33) C2:2 Methyldopa RR 0.31 (0.04-2.65)		
				Preterm birth <37 GW			
				C2 Any hypertensive C2:1 Beta blockers C2:2 Calcium channel blockers	C2 Methyldopa RR 0.76 (0.55-1.05) C2:1 Methyldopa RR 0.81 (0.57-1.15) C2:2 Methyldopa RR 0.53 (0.24-1.17)		
				SGA			

				C2 Any hypertensive C2:1 Beta blockers C2:2 Calcium channel blockers	C2 Methyldopa RR 0.80 (0.53-1.21) C2:1 Methyldopa RR 0.85 (0.55-1.32) C2:2 Methyldopa RR 0.4 (0.10-1.60)		
				I: Antihypertensive therapy (any, glyceryl trinitrate or betablockers	C:3 (Calcium channel blockers)		
				Any fetal/ neonatal death incl miscarriage			
				C3 Anyhypertensive C3:1 Glyceryl trinitrate C3:2 Beta blockers	C3 Calcium channel blockers RR 1.0 (0.06-15.55) C3:1 calcium channel blockers RR 0.0 (0.0-0.0) C3:2 calcium channel blockers RR 1.0 (0.06-15.55)		
				Preterm birth			
				C3 Any hypertensive C3:1 Glyceryl trinitrate C3:2 Beta blockers	C3 Calcium channel blockers RR 0.63 (0.20-1.91) C3:1 Calcium channel blockers RR 0.63 (0.20-1.91) C3:2 Calcium channel blockers NA		
				SGA			

				C3 Any hypertensive C3:1 Glyceryl trinitrate C3:2 Beta blockers	C3 Calcium channel blockers RR 1.0 (0.10-9.96) C3:1 Calcium channel blockers RR 1.0 (0.10-9.96) C3:2 Calcium channel blockers NA		
Churchill et al, 2013 Cochrane	SR	4 RCTs 425 women		Stillbirth		Interventionist care was: either induction of labour or caesarean section after corticosteroids to improve fetal lung maturation, (in practice after 24 to 48 hours). Expectant care was: corticosteroids, stabilization of the woman's condition and then, aim to delay delivery. Primary child outcomes were stillbirth, neonatal death, IVH and or HIE. Secondary outcomes were low Apgar score at five minutes, neonatal seizures, hyaline membrane disease, pneumothorax, necrotising enterocolitis, ventilation, measures of long-term growth and development, such as important impairment and cerebral palsy, small-for-gestational age, gestation at birth. Babies in the expectant management group were less likely to have hyaline	High
				Interventionist 1/222	Expectancy 6/203 RR 0.20 (0.03-1.16)		
				Neonatal death			
				Interventionist 30/222	Expectancy 20/201 RR 1.33 (0.80-2.23)		
				IVH and/or HIE			
				Interventionist 34/141	Expectancy 16/121 RR 1.82 (1.05-3.14)		

						membrane disease, need ventilation, had higher gestational age at birth, less need for NICU, shorter stay at NICU, but were more SGA than babies in the interventionist group	
Cluver et al, 2017, Cochrane	SR	5 RCTs, 1891 women		Composite infant mortality and severe morbidity: not enough data (a high level of heterogeneity between the two studies in this analysis so data was not pooled) There were no clear differences between subgroups based on our subgroup analysis by gestational age, gestational week or condition. Planned early delivery was associated with higher levels of respiratory distress syndrome (RR 2.24, 95% CI 1.20 to 4.18, three studies, 1511 infants), and NICU admission (RR 1.65, 95% CI 1.13 to 2.40, four studies, 1585 infants). for the baby Not significant difference in hospital stay: (MD -0.20 days, 95% CI -0.57 to 0.17, one study, 756 infants, evidence graded moderate).			High
Crowther Cochrane. 2015	SR	10 RCTs 4733 women		Respiratory distress syndrome		Women considered to be at risk of preterm birth who had received a single course of prenatal corticosteroid seven or more days previously were included. Significant differences were found for birth weight and SGA (lower mean birth weight (76g) and increased rate of babies being SGA with repeat steroids). No differences in other primary outcomes including mortality, chronic lung disease, IVH and disability at childhood follow up. No	High
				Repeat doses >7 days 365/1272	Single course 426/1266 RR 0.86 (0.77-0.96)		
				Composite serious infant outcome			
				Repeat doses >7 days 200/1121	Single course 256/1111 RR 0.78 (0.66-0.91)		

						significant differences for secondary outcomes including growth, blindness, deafness, CP, neurodevelopment.	
Duley, 2013 Cochrane	SR	35 RCTs. Totally 3573women with very high blood pressure, sBP ≥170 or dBP ≥105 mm Hg		Labetalol versus hydralazine Fetal or neonatal death 3/141 | 4/133 RR 0.75 (0.17-3.21) No other significant differences or secondary outcomes including PTB; IRDS, NEC, ROP, IVH, Apgar score and long term outcomes Labetalol versus calcium channel blockers 5 trials, 171 women No significant difference for neonatal outcomes, but few events and wide CIs Labetalol versus methyldopa 1 trial, 74 women Insufficient data to assess neonatal outcomes Calcium channel blockers versus hydralazin 8 trials, 404 women No significant difference for neonatal outcomes, but few events and wide CIs		Author's conclusion: "The choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug; on what is known about adverse effects; and on women's preferences. Exceptions are nimodipine, magnesium sulphate (although this is indicated for women who require an anticonvulsant for prevention or treatment of eclampsia), diazoxide and ketanserin, which are probably best avoided."	AMSTAR High
Firoz, 2014, Canada	SR	16 RCTs, 15 during pregnancy (914 women) and one postpartum (38 women) with very high BP (sBP ≥160 mmHg and/or dBP ≥110 mmHg		Single oral antihypertensive agents: C1Oral/sublingual nifedipine	C1:1Parental hydralazine iv C1:2 Labetalol iv No difference in neonatal outcome (CS, adverse fetal heart effects, Apgar score < 7 at 5 min, perinatal	Conclusion was that there was no difference in neonatal outcome. Inclusion criteria was at least one arm with oral antihypertensive. Overlap with Duley?	High

				C2 Nifedipine capsules C3 Oral labetalol	death, neonatal death or stillbirth C2 Nifedipine tablets No fetal death in either arm. C3 Oral methyldopa No difference in CS or perinatal death.		
Guida et al, 2017, Brazil	SR (2 RCTs and 4 cohort studies)	Women with preterm preeclampsia< 34 GW or between 34 and 37 GW N=183, 703, 670120, 696, 516 and 199, respectively		< 34 GW: Immediate delivery vs expectancy: Perinatal outcomes were worse with immediate delivery 34 – 37 GW: Immediate delivery vs expectancy: Extectant management had better perinatal outcome		No pooled estimates presented	Low
				C2:1 timolol, C2:2oral hydralazine C2:3 oral nifedipine	C2:1: methyldopa C2:2: methyldopa C2:3: methyldopa No neonatal data available		
				C3 Hydralazine iv	C3 Sublingual nifedipine or intravenous labetalol		
Roberts, 2017 Cochrane,	SR (30 RCTs)	7774 women and 8158 infants		Treatment with antenatal corticosteroids (compared with placebo or no treatment) is associated with a reduction in the most serious adverse outcomes related to prematurity, including: perinatal death (risk		Author conclusion: this update supports the continued use of a single course of antenatal corticosteroids to accelerate	High

				ratio (RR) 0.72, 95% CI 0.58 to 0.89) neonatal death (RR 0.69, 95% CI 0.59 to 0.81), RDS (RR 0.66, 95% CI 0.56 to 0.77); moderate/severe RDS (RR 0.59, 95% CI 0.38 to 0.91); intraventricular haemorrhage (IVH) (RR 0.55, 95% CI 0.40 to 0.76), necrotising enterocolitis (RR 0.50, 95% CI 0.32 to 0.78); need for mechanical ventilation (RR 0.68, 95% CI 0.56 to 0.84); and systemic infections in the first 48 hours of life (RR 0.60, 95% CI 0.41 to 0.88).		fetal lung maturation in women at risk of preterm birth. A single course of antenatal corticosteroids could be considered routine for preterm delivery.	
Shekhar, 2015, India	SR	7 RCTs, 363 women with severe hypertension		Oral nifedipine	Labetalol iv	Conclusion was that oral nifedipine is as sate as intravenous labetalol. Primary perinatal outcomes were fetal heart rate (FHR) abnormalities while on treatment, stillbirth and neonatal death. Secondary neonatal outcomes were need for NICU admission and low (< 7) Apgar at 5 minutes. There was no significant difference in low Apgar or NICU admission.	High
				Fetal heart rate abnormalities			
				2/166	8/157 RR 0.31 (0.09-1.11)		
				Stillbirth			
				13/121	18/157 RR 0.66 (0.35-1.27)		
				Neonatal death			
				3/116	10/105 RR 0.27 (0.09-0.87)		
Wang et al 2017 Arch Gynecol Obstet, China	SR (7 RCTs)	1501 women		Ventilatory support (<34 GW)		No difference in fetal or neonatal mortality or NEC (in < 34 or > 34 GW group)	High
				73/161 RR 1.50 (1.11- 2.02	42/139		
				IVH or HIE (<34 GW)			
				38/274 RR 1.94 (1.15-3.28)	17/252		
Original articles n=31							
				Mean prolongation of pregnancy			Low

Astudillo, 2013, Spain	Retrospective observational cohort study	Women with severe PE between 23+6 and 33+6 GW: GrA: Women with concomitant risk factors n=26) GrB: women without risk factors (n=33)		Gr A: mean 8.42 days (SD 7.46; range 2-29 days)	Gr B 10.5 days (SD 8.24; range 2-41 days). P=0.391	Conclusion: Women with severe EO-PE and associated risk factors benefited from expectant management. Concomitant risk factors were associated medical condition, HELLP, severe oligohydramniosis, fetal growth restriction, multiple pregnancies	
				No significant difference in perinatal outcomes between Gr A and Gr B (SGA, Apgar score, jaundice, IRDS, NEC, ROP. IVH , sepsis)			
Bateman et al, 2016, USA	Cohort study, Propensity score (PS) matched 1:3	2 292 116 pregnancies, 10 585 (0.5%) beta-blocker exposed, 2 291 531 non-exposed, matched cohort 10 561 exposed and 31 683 non exposed		Neonatal hypoglycemia (ICD.code) Any betablocker vs no beta-blocker: 4.3% vs 1.2% AOR 1.68 (95% CI 1.50-1.89) Labetalol: AOR 1.78 (95% CI 1.55-2.04) Metoprolol: AOR 1.64 (95% CI 1.15-2.33) Atenolol: AOR 1.54 (0.99-2.4)		Propensity score matching for maternal demographics, obstetric and medical conditions and exposure to other medication, Sensitivity analysis with methyldopa as reference, and within subgroups as women with diabetes, term delivery showed similar results.	Medium
				Neonatal bradycardia (ICD code) Any betablocker vs no beta-blocker: 1.6% vs 0.5% AOR 1.29 (95% CI 1.07-1.55) Labetalol: AOR 1.34 (95% CI 1.08-1.67) Metoprolol: AOR 0.59 (95% CI 0.32-1.09) Atenolol: AOR 1.16 (0.60-2.27)			
Bergman et al, 2017 EUROCAT	Case-malformed control study	117 122 registrations of congenital malformations,		No association with beta-blockers and previously reported anomalies (neural tube defects, cleft lip with or without cleft palate, cleft palate, congenital heart defects, hypospadias) for any beta-blocker, or		Case-malformed control study design (limited recall or information bias, but results not	Medium

		49 243 had signal anomalies, controls were 50 709 with non-chromosomal, non-signal anomalies and 17 170 with chromosomal anomalies. 320 (0.27%) exposed to beta-blockers in first trimester		non selective, selective or combined alfa-and beta-blocker. The exploratory analysis showed an association with multicystic renal dysplasia for any beta-blocker (9 cases) AOR 2.5 (95% CI 1.3-5.1) and for combined alfa-and beta-blocker (4 cases) AOR 3.8 (1.3-11.0)	generalized to the general population. Adjusted for centre, year of birth, pregnancy outcome, use of other hypertensive agents and maternal age	
Broekhuijsen, 2015, the Netherlands	Retrospective cohort study	Chronic hypertension: 3457 women Controls: 984 932 normotensive women		Composite adverse neonatal outcome 85/3 457 vs 21 556/984 93 AOR 0.8 (0.6-1.0) Neonatal morbidity 602/3 457 vs 130 264/ 984 932 AOR 1.2 (1.1-1.4)	Conclusion: Optimal time for delivery for women with chronic hypertension is between 38 and 40 GW. Adverse neonatal outcome was a composite measure of Apgar score <7 at 5 minutes, severe respiratory morbidity, neonatal seizures or perinatal death (stillbirth or neonatal death < 7 days after birth) Neonatal morbidity included SGA, BPD, PVL, HIE etc,	Medium
DelgadoDe Pasquale, 2013, Panama	RCT	261 women with severe hypertension (sBP≥160 mmHg/dBP ≥110 mmHg	19	No child outcome		
Dhananjaya, 2015 India	RCT	Women with BP ≥160/110 mmHg, ≥28 GW	NR	Oral nifedipine (n=30) vs Labetalol iv (n=30)	Neonatal outcomes were secondary outcomes. No	Low

				No difference in mean gestational age, mean birth weight, Apgar score, NICU admission or neonatal mortality	significant difference in neonatal outcome	
Duro-Gomez et al, 2017, Spain	Retrospective cohort study	Nifedipine (N):43 crisis (10 women), Labetalol (L): 12 crisis (4 women)	NR	No difference in neonatal adverse outcomes.	Only 14 women, but 55 crisis	Low
Durst et al, 2016, USA	Retrospective cohort study	320 women: 37+0-37+6: n=67 38+0-38+6: n=76 39+0-39+6: n=177	NR	CS (=primary outcome): 37+0-37+6: 18/67 (26.9%) 38+0-38+6: 15/76 (19.7%) 39+0-39+6: 53/177 (29.9%) p value for trend=0.39 AOR (95% CI) for maternal and neonatal outcomes compared to ≥39 GW Any (neonatal or maternal adverse outcome: 37+0-37+6: 0.60 (0.33-1.10) 38+0-38+6**: 0.50 (0.28-0.90)** Neonatal outcomes were similar among the groups.	Composite maternal outcome included CS, endometritis, PPH, DVT, readmission, BP treatment pp, wound infection, CA. Composite neonatal outcomes included NICU admissions, length of stay ≥5 days, Apgar score at 5 ≤3 RDS or death. Any adverse outcome was any adverse maternal or neonatal outcome Adjusted for BMI	Low
Fisher et al, 2017, USA	Case control study	10 645 congenital heart defects (CHD) cases and 11 137 non malformed controls randomly selected from birth certificates Early pregnancy: Exposed n=164, controls n=102, late pregnancy;		Any early pregnancy antihypertensive medication: Any CHD: AOR 1.59 (95% CI 1.23-2.05) Untreated hypertension: Any CHD: AOR 1.23 (1.11-1.36) Any late pregnancy antihypertensive medication: Any CHD: AOR 1.78 (95% CI 1.32-2.40) Any early pregnancy antihypertensive medication: Coarctatio aortae: AOR 2.50 (95% CI 1.52-4.11) Pulmonary valve stenosis: AOR 2.19 (95% CI 1.44-3.34) Perimembranous ventricular septal defect: AOR 1.90 (95% CI 1.09-3.31)	Confounding by underlying disease cannot be ruled out. Few cases in each subgroup of CHD	Medium

		Exposed n=122, controls n=72		Secundum atrial septal defect AOR 1.94 (95% CI 1.36-2.79) Beta-blockers and renin-angiotensin system blockers were associated with these specific CHDs (not coarctatio for renin-angiotensin system blocker) and any CHD		
Harper et al, 2016, USA	Retrospective cohort study	Women with a live singleton pregnancy reaching ≥36 GW and chronic hypertension: All, (planned delivery vs expectant management) 36 GW n=683 (20 vs 663), 37 GW n= 572 (39 vs 533), 38 GW n= 414 (30 vs 384) and 39 GW n= 280 (124 vs 156)		Planned early deliveries vs late planned deliveries: Primary neonatal outcome <37 GW vs ≥37 GW; 10.0% vs 2.6%, p=0.04 38+0 -38+6 GW vs ≥38+0 GW: 0 vs 2.3%%, NS Planned 36-38+6 GW vs ≥39+0 GW 4.5% vs 2.5% AOR 1.9 (95% CI 0.6-5.9) Perinatal death NS	Adjusted for parity, smokiung	Medium
Kawakita et al, 2018, USA	Retrospective cohort study	Women with PE (mild or severe), ≥ 34 GW, singleton pregnancy IOL: n=5104 CS: n= 402	NR	IOL (induction of labour) vs planned CS: Composite neonatal outcome: 0.7% vs 1.2% AOR: 0.32(95% CI: 0.10–0.99) NICU admission: 16.2% vs 26.6% AOR: 0.60 (95% CI: 0.43–0.84) TTN: 3.9% vs 8.5% AOR: 0.38 (95% CI: 0.22–0.64) RDS: 2.1% vs 5.2% AOR: 0.44 (95%CI: 0.22–0.86) Composite neonatal outcome for nulliparous: 0.8% vs 1.5% AOR: 0.23(95% CI: 0.07–0.80)	Stratification for parity Adjusted for age, race/ethnicity, marital status, insurance type, hospital type, diabetes (preexisting or gestational), gestational age, body mass index, and type of preeclampsia (planned CS as referent).	Medium

				NS for multiparous		
Madazli, 2013, Turkey	Cohort study	144 women, (early onset preeclampsia [EO-PE]=91 [45 mild and 46 severe] and late onset preeclampsia [LO-PE]=63 [34 mild and 29 severe])	NR	EO-PE Mild PE (n=45) vs Severe PE (n=46) No significant differences between low Apgar score, abnormal Ut artery Doppler, birth weight , SGA, stillbirth and early neonatal death LO-PE Mild PE (n=34) vs Severe PE (n=29) No significant differences between low Apgar score, abnormal Ut artery Doppler, birth weight, SGA, stillbirth and early neonatal death	Rates of SGA, oligohydramniosis, Apgar score < 7 at 5 minutes, stillbirth and early neonatal death was higher in EO-PE than in LO-PE (p<0.001)	Low
Magee, 2015 International study (CHIPS trial)	RCT	1030 women with nonprotein-uric preexisting or gestational hypertension	49	Primary outcome (miscarriage, ectopic pregnancy, pregnancy termination, stillbirth or neonatal mortality) or high level neonatal care (more than 48 hours) Less-tight control 155/493 / Tight control 150/488 AOR 1.02 (0.77-1.35) Pregnancy loss (miscarriage, ectopic pregnancy, pregnancy termination, stillbirth or neonatal mortality) Less-tight control 15/493 / Tight control 13/488 AOR 1.14 (0.53-2.45) High level neonatal care (more than 48 hours)	There was no significant difference between less-tight and tight control for any neonatal outcome. Primary outcome was a composite of pregnancy loss (miscarriage, ectopic pregnancy, pregnancy termination, stillbirth or neonatal mortality) or high level neonatal care (more than 48 hours).Other outcomes included components of the primary outcomes, measurements of fetal growth	High

				Less-tight control 141/480	Tight control 139/479 AOR 1.00 (0.75-1.33)	(SGA) and newborn complications. Adjusted for type of hypertension (preexisting vs gestational), center, use of antihypertensive therapy at randomization, previous BP of 160/110 mmHg or higher during the pregnancy, gestational diabetes, gestational age at randomisation	
				SGA			
				Less-tight control <10th percentile 79/491 <3rd percentile 23/491	Tight control <10th percentile 96/488 AOR 0.78 (0.56-1.08) <3rd percentile 26/491 AOR 0.92 (0.51-1.63)		
Magee, 2016a International study (CHIPS trial), BJOG	Cohort study.Secondary analysis of CHIPS trial (RCT)	481/987 CHIPS recruits at randomisati and 657/987 CHIPS recruits postrandomisation		At randomization Methyldopa vs Labetalol		Primary outcome definition, see Magee 2015 above. Women treated with methyldopa versus labetalol (particularly those with pre-existing hypertension) may have better outcomes (significantly less babies with birth weight < 10th centile and also preterm birth < 34 and 37 wks postrandomisation), Adjusted for allocation group, type of hypertension (preexisting vs gestational), center, use of antihypertensive therapy at randomization, previous BP of 160/110 mmHg or higher during the pregnancy, gestational age at randomization and for the postrandomisation analysis whether women were on antihypertensive at randomization (yes/no)	High
				Primary outcome			
				67/241	93/237 AOR 0.68 (0.42-1.10)		
				Birth weight <10 centile			
				30/240	51/234 AOR 0.48 (0.26-0.87)		
				Post- randomization before delivery Methyldopa vs Labetalol			
				Primary outcome			
				58/224	162/433 AOR 0.63 (0.40-1.00)		
				Birth weight <10th centile			
				32/223	91/430 AOR 0.54 (0.32-0.92)		

Magee, 2016b International study (CHIPS trial), BJOG	Cohort study.Secon-dary analysis (RCT)	566/987 CHIPS recruits at randomisation and 815 /987 CHIPS recruits postrandomisation		At randomization Less-tight vs tight. Methyldopa (MD) and labetalol (LB)		Primary outcome definition, see Magee 2015 above. Outcomes for "less-tight" versus "tight" control were not dependent on use of MD or LB, both for considering the use of LB or MD before or after randomization. Adjusted for type of hypertension (preexisting vs gestational), center, use of antihypertensive therapy at randomization, previous BP of 160/110 mmHg or higher during the pregnancy, gestational age at randomization and for the postrandomisation analysis whether women were on antihypertensive at randomization (yes/no)	High
				Primary outcome			
				LB 42/110 MD 40/125	LB 51/127 AOR 0.92 (0.53-1.62) MD 27/116 1.56 (0.86-2.83)		
				Birth weight <10th centile			
				LB 20/108 MD 15/125	LB 31/126 AOR 0.67 (0.35-1.30) MD 15/115 AOR 0.80 (0.36-1.76)		
				Post- randomization before delivery Less-tight vs tight			
				Primary outcome			
				LB 79/186 MD 27/98	LB 83/247 AOR 1.38 (0.91-2.10) MD 31/126 AOR 1.15 (0.61-2.16)		
				Birth weight <10th centile			
				LB 37/183 MD 11/98	LB 54/247 AOR 0.93 (0.57-1.50) MD 21/125 AOR 0.65 (0.29-1.45)		
McKinney et al, 2016, AJOG, USA	Retrospectiv e single center cohort study	60 women with PE and FGR and 139 with PE and no FGR		No FGR vs FGR		FGR was associated with a shorter interval to delivery (see maternal outcome). Admission to NICU, neonatal length of stay and NNM were higher when there was FGR, but after logistic regression analysis these associations were no longer significant.	Low
				BW 1810 g ±736 SGA 26/139 NNM 6/139 NICU 106/139 NICU stay, d, median (IQR): 14 (10-18)	BW 992±437, p<0.001 SGA37/60, p<0.001 NNM 8/60, p<0.02 NICU 58/60, p=0.001 NICU stay, d, median (IQR): 44 (27-64), p<0.001		

				No FGR vs FGR Logistic regression analysis		Onset of PE was < 34 GW Adjustment: maternal race, smoking, chronic hypertension, GA at delivery, severe PE, fetal sex	
				NNM 6/139 NICU 106/139	NNM 8/60 AOR 1.06 (0.53-2.13) NICU 58/60 AOR 1.74 (0.80-3.78		
Noijj, 2014 The Netherlands	Retrospective nested case control study and meta-analysis (2 RCTs)	Labetalol 76, nicardipine 99		Labetalol vs nicardipine		Conclusion was that labetalol had more neonatal side effects (although not significant)!! Dysmaturity was defined as a birth weight < p2.3.	Low
				Dysmaturity 9/76 BW 2590±929 g	Dysmaturity 11/99 p=0.889 BW 2673±708 g p=0.497		
				Other neonatal side effects (hypoglycemia, hypotension and respiratory problems) (only in retrospective study and not in MA) were not significant different. No figures shown.			
Orbach, 2013, Israel	Retrospective cohort study	CTN and no antihypertensive therapy n=1074 women. CTN with antihypertensive therapy in the 1st trimester n=620 women (atenolol +methyldopa [MD] n=271, MD n=114, atenolol n=188)		Preterm delivery (without hypertension as reference)		Chronic hypertension with or without treatment during pregnancy is an independent and significant risk factor for adverse neonatal outcomes, the risk was lower among non-treated than among treated women. Both methyldopa and atenolol was associated with adverse outcomes. The exposed group were women with antihypertensive treatment (methyldopa or atenolol) during the first trimester. Methyldopa	Medium
				Non-treated hypertension	AOR 1.89 (1.59-2.25)		
				Exposure to MD or atenolol	AOR 3.23 (2.57-4.05)		
				SGA (without hypertension as reference)			
				Non-treated hypertension	AOR 2.06 (1.44-2.95)		
				Exposure to MD or atenolol	AOR 2.25 (1.29-3.94)		
				IUGR (without hypertension as reference)			
				Non-treated hypertension	AOR 2.09 (1.51-2.89)		

		No CTN: 97 820 women		Exposure to MD or atenolol	AOR 4.40 (3.02-6.40)	and atenolol were also assessed individually. Adjustment for maternal age, ethnicity, smoking, diabetes mellitus, twin pregnancy lack of perinatal care and parity,	
Owens et al, 2014 Journal of the Mississippi Med Assoc	RCT	Immediate delivery: n=94 Expectancy: n=75	3 and 11	Immediate delivery (within 12 hours)	Immediate vs Expectancy: Birth weight 2491(426) vs 2766 (509)g p=0.01 NS for other neonatal outcomes incl NICU and NICU stay	Study stopped at 183/ 220 patients	Low
Patel et al, 2017, India, The J Ob Gyn India	RCT	I= 76 (hydralazine) C=76 (labetalol)	No	Fetal and neonatal outcomes were similar (Fetal heart rate abnormalities, Apgar, NICU, stillbirth)		Not blinded	Low
Sabir et al, 2016, Pakistan, J Postgrad Med Inst	Quasi RCT	I=50 nifedipine, C=50 hydralazine	No	Fetal heart rate abnormalities were similar 3/50 and 1/50 respectively		Not blinded	Low
Schoen et al, 2017, USA and Italy, J Mat Fetal Med	Retrospective cohort study	365 singleton pregnancies with superimposed PE, 198 outpatients and 167 inpatients		Fetuses from women in the outpatient group had a significantly lower risk of small for gestational age (17.7%versus 29.3%; aOR 0.53, 95%CI 0.30–0.84), and lower risk of admission to neonatal intensive care unit (40.4% versus 47.9%; aOR 0.72, 95%CI 0.39–0.95) compared to women managed as inpatients.		Adjusted for age, BMI, parity, smoking, ethnicity, antihypertensive drug use, concomitant diseases	Medium
Sharma et al, 2017, India, AJOG	RCT	I=30 hydralazine C=30 nifedipine	No	Apgar, NICU and birthweight were similar in both groups		Blinded	High
Sharma et al, 2016, Hypertension Pregnancy	Retrospective cohort study	I=30 labetalol C=69 hydralazine	N=17	Fetal heart trace (FHT) available for 82 women: No difference between groups, no category III trace, no women delivered because of FHT abnormality. Posttreatment hypotension was associated with increased risk for FHT abnormality 44% vs 14% , OR 5.60 (95% CI 1.26-24.82)			Low
Shi, 2016, China,	RCT	I=iv labetalol	No	No differences in Apgar score or BW		Not blinded	Medium

J Clin Pharm and Therapeutics		C=oral nifedipine				
Su et al, 2013, Taiwan	Cohort study	2727 women with CHT and 8 181 matched controls		LBW <2500g	Women on antihypertensive therapy had higher risk of LBW, PTB and SGA compared to untreated women with CHT. All types of antihypertensives were associated with increased risk for LBW, PTB and SGA but women on vasodilators had the highest risk of LBW, PTB and SGA. Antihypertensive drugs were categorized into 6 types, central α agonists, beta-blockers (BBs) combined α and BBs, calcium channel blockers, diuretics and vasodilators. Women with more than one drug were excluded. Women with PE and gestational hypertension were excluded. Primary outcome was LBW, other outcomes were PTB and SGA. Adjustment for maternal age, parity, education and comorbidity.	Medium
				Non-treated hypertension: AOR 1.47 (1.13-1.91) Exposure to antihypertensive drugs: AOR 2.29 (1.95-2.68)		
				Preterm birth <37 GW		
				Non-treated hypertension: AOR 1.30 (1.01-1.66) Exposure to antihypertensive drugs: AOR 2.18 (1.89-2.52)		
				SGA		
				Non-treated hypertension: AOR 1.27 (1.07-1.52) Exposure to antihypertensive drugs: AOR 1.62 (1.45-1.81)		
Van Oostward et al, 2017 The Netherlands, BJOG	Case series	n=140 children		Neonatal survival was poor (19%), and was worse (6.6%) if the mother was admitted before 24 weeks of gestation. Complications occurred frequently among survivors (84%). After active support (in 36%), neonatal survival was 54%.		Low

Wang et al, 2017. China, J Clin Hypertension	RCT	Labetalol n=72 Nifedipine n=71		Apgar score >7 Nifedipine 66/71, labetalol 68/72 RR 0.98 95% CI 0.90-1.07) NS birth weight		Randomisation not presented. Placebo controlled, blinded, no demographics presented.	Medium
Webster et al, 2017, UK, Hypertension	RCT	Labetalol 56 Nifedipine 58	2	NS difference in birth weight, adjusted mean difference -240 g(-590 to 110 g) Any adverse neonatal effect in 11 (22%) in labetalol and in 17 (33%) in nifedipine group. Admittance to NICU 11 (22%) vs 15 (29%) NS		No statistics for adverse outcomes, given the study was not powered for this. Not blinded	Medium
Xie et al, 2014, Canada	Retrospective cohort study	Women with HDP: I=betablocker (BB) n=416 C=methyldopa only n=1000		All hypertensive disorders in pregnancy (HDP) BB vs MD		Women with chronic hypertension (CH) and BBs vs women with CH and MD had higher risk of SGA<10th centile and SGA<3rd centile and neonatal hospitalitzation (also adjusted for time of starting treatment). Women with CH, gestational hypertension and PE were included. Main outcomes were SGA < 10th and <3rd centile, PTB, hospitalization for IRDS, sepsis, or seizures, stillbirth and infant death. Adjustment for maternal age, parity, birth year and HDP	Medium
				SGA <10th centiles 17.3%	SGA <10th centiles 14.5% AOR 1.24 (0.90-1.70)		
				SGA <3rd centiles 5.5%	SGA <3rd centiles 5.5% AOR 0.99 (0.59-1.66)		
				PTB 24.3%	PTB 26.9% AOR 0.84 (0.64-1.10)		
				Stillbirth 0.96%	Stillbirth 0.40% AOR 2.25 (0.54-9,36)		
				Infant death 0.48%	Infant death 0,60% AOR 0.88 (0.17-4.50)		
				Hospitalization for IRDS, sepsis or seizures 5.5%	Hospitalization for IRDS, sepsis or seizures 3.9% AOR 1.40 (0.82-2.39)		
Zhu et al, 2017, China, Int J Clin Exp Med	RCT	I: labetalol + Mg n= 60, C: nifedipine + Mg n=60	No	Apgar score lower and more neonatal asphyxia in nifedipine group vs labetalol group		Randomisation unclear, not blinded, gestational age at delivery unclear	Low

8. Magnesiumsulfat regimer

Systematic reviews n=4 **Treatment of preeclampsia/eclampsia** **Magnesium sulfate regimens for treatment of eclampsia or preeclampsia n=14** **Outcome variable: Efficacy: Prevention of eclampsia or prevention of recurrent seizures in women with eclampsia after post-treatment initiation, Pharmacokinetics**							
Author, year, country	**Study design**	**Number of studies/ patients**	**With drawals - dropouts**	**Results**		**Comments**	
				Intervention	Control		
Bain, 2012, BMC Pregnancy and Childbirth	SR	143, 21 RCTs, 15 nonrandomised, 32 case series, 75 reports	NR	Compared with placebo or no treatment MgSO4was not associated with an increased risk of maternal death, cardiac arrest or respiratory arrest. MgSO4 significantly increased the risk of any adverse effects overall, (RR 4.62: 95% CI 2.42-8.83, 4 trials, 13 322 women) and treament cessation due to adverse effects (RR 2.77; ; 95% CI 2.32-3.30, 5 trials, 13 666 women). Few subgroup differences were observed between regimens. In one trial low dose compared to high dose reduced treatment cessation (RR 0.05; 95% CI 0.01-0.039, 126 women. Case reports supported an association between overdose and life threatening consequences			Overall quality of the SR: Medium according to AMSTAR
Gordon, 2014 JOGC	SR	26 (10 RCT, 16 observational studies) 4688 women	NR	Eclampsia 0.0-26.5%, median 3% 14 g MgSO4 (Pritchard loading dose*: 4 g iv + 10 g im) vs standard Pritchard* regimen: 4 RCT, 396 women with eclampsia or preeclampsia: Eclampsia occurrence or recurrence: RR 1.64 (95% CI 0.48-5.65)		Studies performed in low and middle income countries. HDP often not well defined. 39 different MgSO4 regimens, 22/25 studies evaluated reduced dose or duration of treatment.	Overall quality of the SR: Low according to AMSTAR

				10 g MgSO4 as loading dose vs standard Pritchard* regimen): 1 RCT, 103 women with eclampsia or preeclampsia: Eclampsia occurrence: p=0.142, recurrence; p=0.195. 1 observational study (Bangladesh), 265 women with eclampsia obtained MgSO4, 10 g loading dose (4 g iv+ 6 g im) in their home vs no treatment followed by referral: Eclampsia recurrence: RR 0.23 (95% CI 0.11-0.49) No other statistics in the article.		
Pratt, 2015 AOGS	SR	5 non RCT (quasi-RCT, cohort, case-control, cross-sectional	NR	Seizures post-treatment initiation: Low dose vs Pritchard*: 5 studies (3 eclampsia, 2 preeclampsia) 899 women: OR 1.02 (95% CI 0.46-2.28) Loading dose vs Pritchard*: 2 studies (1 eclampsia, 1 preeclampsia) 146 women: OR 0.99 (0.22-4.50)	Included studies of low or very low quality. Definitions of HDP not always clear.	Overall quality of the SR: Medium according to AMSTAR
Vigil de Garcia and Kudmir, 2014 J Mat Fetal and Neonatal med	SR	2 RCT	NR	MgSO4 vs other therapy/no therapy/placebo in women with severe PE or eclampsia *diagnosed postpartum* No difference in eclampsia (one trial, Magpie) For seizure recurrence MgSO4 was superior to diazepam, but no difference to phenytoin, (Coll trial)	Not MgSO4 regimen	Low
Original articles (RCTs or cohort studies) n=10 (eclampsia n=1, magnesium sulfate regimens n= 9)						
Lal, 2013, Pregn Hypertension	Cohort (eclampsia			Women with eclampsia (n=191) vs women with preeclampsia (n=7012) Maternal outcomes Cesarean section 48.7% vs 35.7%, OR 1.71 (95% CI) 1.28-2.28) Postpartum blood transfusion 7.0% vs 5.1%, OR 1.41 (95% CI 0.56-3.52) Maternal ICU admission 9.4% vs 0.8%; OR 12.88 (95% CI 7.0 vs 23.7)	Rate of eclampsia 0.08%	Low

Abdul, 2013 Arch Gyn Ob	RCT	72 women	0?	Low dose: Recurrent seizures: 2/39	Pritchard: Recurrent seizures: 1/33	Women with eclampsia antepartum, intrapartum or postpartum. Rate of eclampsia 4.2%	Low
				p=0.587			
Anjum, 2016 Arch Gyn Ob	RCT (quasi randomised)	208 women	15 women with complicated eclampsia was excluded	12 hour MgSO4 1g/h regimen Recurrent seizures post treatment: 0/132	24 hour MgSO4 1g/h regimen. Recurrent seizures posttreatment: 0/76	Women with eclampsia antepartum, intrapartum or postpartum First 6 months control group, then 6 months intervention etc. Rate of eclampsia: 3.9%	Low
				No recurrent seizures in either group after completion of MgSO4 for 12 or 24 hours.			
Anjum, 2016 Int J Gyn Ob	RCT? No details about randomisation	119 women	15 women with elevated serum creatinine Or previous eclampsia were excluded	Zuspan** regimen +6 hour MgSO4 1 g/h after delivery Seizures posttreatment: 0/76	Zuspan* regimen + 24 hour MgSO4 1 g/h after delivery Seizures posttreatment: 0/43	Women with severe preeclampsia postpartum. In correct number of patients (should be 119-15=104, now 119)	Low
				No recurrent seizures in either group after completion of MgSO4 for 6 or 24 hours.			
Brookfield, 2016 AJOG	Cohort study	111 women	Women on dialysis	Pharmacokinetics of MGSO4, (serum magnesium levels) influenced by maternal weight and presence of preeclampsia (n=92, 83%)			Medium
Charoenvidhya and Manotaya, 2013, J med Assoc Thai, Thailand	RCT	60 women		A maintenance dose at 2 g/hour was more likely to attain the therapeutic level of serum magnesium when compared to 1g/hour with no difference in maternal and neonatal outcome			Low
Jana, 2013 Int J Gyn Ob	Cohort study	554 women	NR	Low dose MgSO4 regimen No of recurrent seizures: 34/554 (6.1%)	Pritchard regimen No of recurrent seizures: 82/841 (9.7%)	Women with eclampsia. First period 2001-2001 compared with the Collaborative Eclampsia Trial. Second period (n=841)	Low

				p=0.02			
	Case series	2929 women	NR	Low dose MgSO4 regimen No of recurrent seizures NR	No control group	Retrospective study 2003-2011	
Kashanian, 2015 J Mat Fetal Med Neonatal Med	RCT	182 women	0	12 h MgSO4 maintenance (5 g im /4 h): Seizures: 1/79	24 h MgSO4 maintenance (5 g im /4 h) Seizures: 0/91	Women with severe preeclampsia postpartum	Medium
				p=1.0			
Maia, 2014 Int J Gyn Ob	RCT	120 women	Protocol violation: 2, Excluded during monitoring:6	12 h MgSO4 maintenance (1 g/h): Seizures: 0/56	24 h MgSO4 maintenance (1 g/h) Seizures: 0/56	Women with severe preeclampsia postpartum	Medium
				p=1.0			
Salinger et al 2013 BJOG, India	Part of RCT	258 women		Pharmacokinetic study (part of an RCT) A larger loading dose (6 g) for the Iv regimen should be considered, the iv loading dose provided lower initial concentration than the im regimen. Serum levels were low and possible subtherapeutic in a significant proportion of the women			Medium

NR not reported, SR systematic review, RCT randomized controlled trial, OR odds ratio, CI confidence interval, AMSTAR, *standard Pritchard MgSO4 regimen: loading dose 4 g +10 g im (5 mg im in each buttock) followed by maintenance dose of 5 g im every 4 h (see Pratt AOGS 2015), *standard Zuspan MgSO4 regimen: loading dose 4 g iv, followed by maintenance dose of 1 g/h iv infusion ((see Pratt AOGS 2015)

9. Magnesiumsulfat, neonatal effekt

Treatment of preeclampsia/eclampsia, SR no 2 **Magnesium sulfate regimens for treatment of eclampsia or preeclampsia n=5** **Outcome variable: Child outcomes**							
Author, Year, Country	**Study design**	**Number of studies/ patients**	**With drawals - dropouts**	**Results**		**Comments**	**Quality High Medium Low**
				Intervention	**Control**		
Gordon, 2014 JOGC	SR	26 (10 RCT, 16 observational studies) 4688 women	NR	Eclampsia 0.0-26.5%, median 3% Perinatal mortality 2%-65.4%, median 20% Stillbirth 1.5% - 55.4%, median 11.4% Neonatal mortality 4.6% - 30.8%, median 10%		Studies performed in low and middle income countries. HDP often not well defined. 39 different MgSO4 regimens, 22/25 studies evaluated reduced dose or duration of treatment.	Overall quality of the SR: Low according to AMSTAR
Pratt, 2015 AOGS	SR	5 non RCT (quasi-RCT, cohort, case-control, cross-sectional	NR	Fetal and/or neonatal mortality Low dose vs Pritchard*: 4 studies, 800 participants: OR 0.87 (95% CI 0.38-2) Loading dose vs Pritchard*: 2 studies (1 eclampsia, 1 preeclampsia) 147 participants: OR 0.49 (0.23-1.03)		Included studies of low or very low quality. Definitions of HDP not always clear.	Overall quality of the SR: Medium according to AMSTAR
Original articles (RCTs or cohort studies) n=3 (eclampsia 1, magnesium sulfate regimens 2)							
Lal, 2013, Pregnancy Hypertension, USA	Cohort,			Women with eclampsia (n=191) versus women with preeclampsia (n=7012)		Rate of eclampsia 0.08%	Low

	(Eclampsia)			Cord arterial pH 7.19 (0.12) vs 7.22 (0.10) p<0.01 (adj BW and GA) 5 min Apgar 8.4 (1.2) vs 8.7 (0.8) p=0.01 (adj) Mechanical ventilation 9.4% vs 3.6%, AOR 1.68 (95% CI 0.88-3.23) NICU admission 37.7% vs 25.8%, AOR 1.15 (95% CI 0.77-1.72) RDS 10.0% vs 5.4%; AOR 5.53 (95% CI 1.11-27.66) ICH 1.6% vs 0.4%, AOR 2.63 (95% CI 5.53 (95% CI 1.11-27.68) Seizures 2.6% vs 0.2%; AOR 10.26 (95% CI 3.12-33.08) Death 0 vs 0		
Abdul, 2013 Arch Gyn Ob	RCT	72 women	0?	Low dose regimen	Pritchard regimen	Women with eclampsia antepartum, intrapartum or postpartum. Rate of eclampsia 4.2%	Low
				Mean (SD) Apgar score at 5 min 5.2 (3.3) vs 6.7 (2.4), p= 0.186 Perinatal mortality 9 vs 5, p=0.129			
Charoenvidhya and Manotaya, 2013, J Med Assoc Thai, Thailand	RCT	60 women		A maintenance dose at 2 g/hour was more likely to attain the therapeutic level of serum magnesium when compared to 1g/hour with no difference in maternal and neonatal outcome			Low

NR not reported, SR systematic review, RCT randomized controlled trial, OR odds ratio, CI confidence interval, AMSTAR, *standard Pritchard MgSO4 regimen: loading dose 4 g +10 g im (5 mg im in each buttock) followed by maintenance dose of 5 g im every 4 h (see Pratt AOGS 2015), *standard Zuspan MgSO4 regimen: loading dose 4 g iv, followed by maintenance dose of 1 g/h iv infusion ((see Pratt AOGS 2015)

10. PRES

Outcome variable: PRES (n=11)							
Author, year, counry	**Study design**	**patients n**	**withdrawal**	**Results**		**Comments**	**Quality**
Fairhall, 2009, Australia	narrative review	NA	NA	Education as a book about IC bleeding and its management		IC bleeding was not on our PICO.	moderate
Brewer, 2013, USA	Single centre retro-spective cohort preeclampsia and eclampsia	n=47 eclamptic patients 46 PRES	0 n=9 missing for return to normal	Antepartum n(%) Diagnosis MR without contrast 20 (87) MR with contrast 14 (81) CT without contrast 8(35) CT with contrast 3(13) MRA/MRV 1(4) Site of lesion	Postpartum n(%) Diagnosis MR without contrast 21(88) MR with contrast 13(54) CT without contrast 8(33) CT with contrast 4(17) MRA/MRV 1(4) Site of lesion	Most African-American (83/79%, ap/PP) Diagnosis MR and CT Morbidity Treatment Time to normal 9-135hours , steroids efter eclampsia 17 hours	low

				Occipital lobe 18(78) Parietal lobe 17(74) Temporal lobe 6(26) Frontal lobe 12(52) Basal ganglia/cerebellum 5(22) Multiple areas 20(87) Treatment n=19 Magnesium sulfate 19(100) Antihypertensives 17(89) Diuretics 13(68) Steroids 13(68) Headache 87,2 % Altered mental status 51,1 Visual dis 34	Occipital lobe 17(71) Parietal lobe 19(79) Temporal lobe 7(29) Frontal lobe 17(71) Basal ganglia/cerebellum 6(25) Multiple areas 21(88) Treatment n=19 Magnesium sulfate 19(100) Antihypertensives 16(84) Diuretics 12(63) Steroids 6(32) Clinical symtoms not separated into ap/pp		

				Nausea/vomiting 19,1			
Camara-Lemarroy 2017 Mexico	Retrospective case-control	29 E 30 controls		17/29 PRES , 0 mortality 15/17 normal after 4.4(3.1) days visual dist 23.5% generalized tonic-clonic seizures	higher proteinuria, ALT and LDH low Apgar	MRI location as in other studies 41% ppstpartum 6% hemipares	low (few)
Chen, 2018 USA	SR, meta analyse 6 studies	98 PE 448 patients	121fulltext resulted in 6 studies for meta-analyse	Hemorrhage in PRES bad prognosis Preeclampsia and PRES better recovery Diffusion progress bad prognosis(cytotoxic edema)			moderate
Cozzolino, 2015, Italy	Review (pub med)	28 studies		MRI the gold diagnostic method Treatment MGSO4, antihypertensive drugs and avoid seizures		most case reports	low
Dahiya, 2018, India	prospective	50E 12 PE		Clinical signs unconsciousness severe headache vision disturbances , increased uric acid and creatinine warning signs		wrong population?	low
Demir, 2012 Turkey	prospective	62 PE?		MgSO4 better recovery than mannitol Full recovery 97.1% resp78.9 % p=0.039			moderate

				Duration days in hospital for treatment 4(2) resp 7(9) depending on distribution of drugs in different time periods			
Dong XY, 2017 China	Retrospective chart study	237 76 PRES		$MgSO_4$ BP no correlation platelet lower D-dimer increased and higher	Risk Visual disturbance OR about 3-4 Multiparity OR cytotoxic- at visual dist 2.94	All recovered= reversible lesions.	low
Fang, 2018, China	Retrospective	49 PE/E with PRES		Risk ; irregular prenatal visits Headache, vision, disturbances, seizure parietal-occipital edema more often in PRES		incidence 0.22% of 100	low
Fisher 2015 USA	Single centre retro-spective cohort preeclampsia and eclampsia	PRES n=9 No PRES n=37 5 0f 8 ecclamp tic had PRES 4 of 38 preeclam ptic had PRES	0	PRES n=9 Indication MR; Headache n=23 Altered mental status NA Visual dis 3 Seizure 8 Mean age years 26.0(5.7) Seizure 5(55%)	No PRES n=37 31.6(5.4) p 0.008 3(8.1) p 0.008	MRI, diagnosis, symptoms, Laboratory analyses PRES and preeclampsia	low

				HBP syst at delivery , pp 2 pp3 176(25)mmHg 154(15) 154(23) proetinuria >300mg 9(100%) Platelets< 150 at MRI 3(33.3%) In stay,days 11(6-278) Site of lesion Occipit/parietal 8(88.9%) Temporal lobe 1(11.1) Frontal lobe 5(66.7) Basal ganglia/cerebel 6(66.7) Grey matter 9(100) White (vasogenic edema 7(77.8	156(22) p 0.03 133(22) p 0.02 143(23) p 0.03 22(61.1%) p 0.04 3(8.1%) p 0.04 7(5-41) p 0.02 difference p< 0.001	Vasogenic edema present in PRES and no PRES 100 resp 88.%)	

Junewar 2014 India	Hospital-based prospective observational study	N=45 10 excluded no PRES	Excluded; 9 HELLP 1 cystic granuloma cerebral	MRI positive n=27 Site of lesion (%) 32/35 Occip 100 parietallobe 100 Frontal lobe 88.9 Temporallobe 44.4 Basal ganglia/cerebel 31.2 Other areas 21.8 Hemorrhage 6(22.2%) Cytotoxic edema 33.3% Symptoms; Headache 68.8% Visual dis 28.6 altered sensorium 94.3 Focal neurol deficit 8.6	MRI negative n=8 NS 12.5 p=0.018 50 p=0.006 NS 0 p=0.015 0.74(0.14) p=0.019 6.31(0.76) p=0.003 319(21) p=0.001 Deceased n=6 1.72(0.07) p<0.001 12.9(3.6) p<0.001 532(45) p=0.009	Cranial MR within 1-7 days of onset of symptoms Imaging Demograåhy, lab analyses, Clinical feature Variables for outcome **6/35 died** ; 2 hemorrhage intraparenchym 2 severe cerebral edema herniation 1 acute renal failure 1 pulmonary edema 85.7% primipara! 80% antepartalt Neither blood pressure nor any lab analyses had any correlation to severity of PRES	low

				Status epilepticus 37.1 Crea mg/dl 1.11(0.41) UA mg/dl 9.47(6.31) LDH IU/L 458(107) Variables fr survived n=29 Crea, mg/dl 0.88(0.26) UA, mg/dl 7.89(1.54) LDH IU/L 404.4(109.1) Moderate-severe PRES n=5	n=4 p<0.027		
Kurdoglu 2015 Turkey	Single centre retrospective cohort	n=81 eclamptic patients	NA	PRES Headache 2(4.4) Visual impair 12(26.7)	No PRES 18(50.0) <0.001 2(5.6) p=0.006		low

		n=45 PRES		Headache +visual 27(60.0) Proteinuria mg(day 1378.38 Apgar 5 min mean 6.47 Stillbirth, n =3	 0 p= 0.001 928.89 p = 0.012 7.75 p 0.002 0		

11. HELLP

Outcome: HELLP							
Author, year, country	**Study design**	**Patients n**	**Withdrawals**	**Results**		**Comment**	**Quality**
Asicioglu, 2014, Turkey	Retrospective cohort	141eclampsia without HELLP 78 with HELLP	NA	E with HELLP Thrombocytopenia <0.001 AST/ALT <0.001 LD <0.001	E without HELLP Ablatio OR 0.6(0.3-1.2) CS 0.9(0.8-1.0) DIC 0.3(0.1-0.8) Neonatal death <32w 0.2 (0.04-1.33) over all 0.4(0.2-0.9)	Patients with HELLP and eclampsia, delivered earlier than without HELLP	low-moderate
Cavaignac-Vitalis 2017 France	Retrospective multicenter	118	NA	Active treatment – delivery within 48 h no predisolon sometimes betamethasone (B) maternal mortality 0 PPH 3(3.5%) ascites/pleural effusion	Expectant treatment-betamethasone **all prednisolone** (A) 0 5(16.1%) p < 0.02	Less maternal and neonatal morbidity in expectant group Higher platelets in expectants	low

				0 IRDS,sepsis, NEC,ICH, transfusion, CPAP	3(9.7) p < 0.01 less than active treatment p< 0.05-0.0001	RR PPH 5.38(1.2-24.6) in active group	
Darby et al, 2013 USA	SR retrospective	87 n=54 liver bleeding	NA	Liver bleeding can found in all classes CS 60.9% Fetal loss 24.1%	Liverbleeding can be present before important lab. changes	No controls Time of liver bleeding Review with unclear selection and search string.	low
Ditosheim, 2016 USA	Narative review	NA	NA	Degree of liver function tests, imaging and clinician not well correlated. Subcapsular hematoma may be treasted conservatively		Narrative but lots of knowledge	NA
Erkilinc S, 2017 Turkey	Retrospective cohort study	171	0	12 mg betamethasone $MgSO_4$	Cut off AST 316 U ALT 217 U bilirubin 2.0 ? LDH 1290 platelets $50x10^9/L$	Blood transfusion the most common complication	low
Kinay et al, 2015 Turkey	Retrospective cross-sectional	N=253	NA	<34 gestational weeks severPE(86) HELLP(30) eclampsia 4(4.7)/6(20.0) p 0.03 plac abruptio NS bloodtransf 4(4.7)/8(26.7)p0. 002 caesarean NS	≥ 34 gestational weeks severePE(111) HELLP(26) NS NS 5(4.5)/5(19.2) p 0.022 NS	Maternal and neonatal outcome mostly more severe complications <34gw. Eclampsia risk higher in	low/moderate

				IUFD 12(14%)/5(16.7) Low birth weight 85(98.9)/ /29(96.7) Fetal distress 36/42.4)/11(37.9)	3(2.7) /0/0 p? 51(45.9)/12(46.2) p? 23(20.7)/3/11.5) p?	HELLPsyndrome than SPE<34gv	
Mao and Chen, 2015 China	Systematic overview 8 RCT 7 retrospective	675 cortico-steriods. 787 controls	NA	Corticosteroids, n=675 Maternal morbidity NS Maternal mortality NS Cesarean NS Neonatal morbidity NA Neonatal mortality 4-23% Platelet count increased 38.08(15.71-60.45) p 0.0009 LDH decreased -044(-0.76—0.12) p 0.007 ALT decreased -143.3(-278—8) p 0.04 Blood transfusion decreased 0.42(0.24-0.76) p 0.004	No corticosteroids, n=787	Treatment Low number of intervensions Unknown doses of corticosteroids	moderate

12. PPCM

Outcome **PPCM**					
Authors, years, country	**Study design**	**Patients n**	**Results**	**Comments**	**Quality**
Afana M et al 2016 J Card Fail	Retrospective register study	PPCM n=1337 controls n=4011	PPCM Incidence 0.02% Risk factors; age >35 hypertension, preeclampsia ecklampsia, smoking, diabetis, anemi, thyroid disorder, astma, c.s., early labor, multiple gestation, afro-americans	Treatment not reported	moderate
Barasa A, 2017 Sweden	Retrospective - register	AHF incl PPCM=241 controls=1063	incidence 1/5719 (0.02%) (1/6936-1/4994, increase LMIC Risk; age, BMI, multifetal pregn, hypertension incl PE/E long-time mortality about 4% at 40 months after delivery	9 death of which 4 HF 2 stroke and diabetes 3 non-CVD	moderate
Bello et al, 2013, USA	SR (22 studies)	PPCM= 979	Hypertension 2-78% Preeclampsia 8-78% multiple gestation 9% No difference according to ethnicity	Treatment not reported Association vascular disease and preeclampsia	moderate
De Haas, 2017, The Netherlands	SR (48 studies)	NA	Normal pregnancy; increase in LVM and RWT by 20 and 10% respectively. Hypertension LVM increase 95% and RWT by 56%		moderate
Ersboll As et al 2016	SR	74 studies	Mechanism; high prolactin and sFlt-1? ECHO, MRI for diagnosis	prolactin-vasoinhibin VEGF-sFlt-1	moderate

Denmark		PPCM N=3660+	>20% relapse newpregnancy, advise against pregnancy Mortality 16% at new pregnancy	Treatment bromocriptine? controversies lactation or not	
Esboll AS et al 2017 Denmark	Retrospective register study cohort	PPCM n=61 controls none	LVEF decides outcome short and extended preeclampsia better progn0sis treatment labetalol, (metyldopa), ACE-inhibitors,cabergoline	incidence 1/10149 deliveries	moderate
Kolte D 2014 USA	National database retrospective cohortl	PPCM n=3421	mortality 1.3% Major adverse events 13.5% Increasing number 2004-11 8.5 till 11.8/10 000 incidence 10.3 per 10 000	high incidence	moderate
Krishnamoorth, 2016, USA	Registerdata base	ap=189 perip=887 postp=3741	In-hospital mortality; ap NA perp 0.5% pp 2.1% Asians 8.3% white OR 0.10(0.02-0.59) Afro-Americans increased risk and more PE Hypertension 33% pre-existing , 9.9%PE !!		moderate
Lima, 2015, USA	Register-data base	2078 cardiomyopathy controls=4 438 439	CMP increased risk major adverse clinical events at delivery Eclampsia, CMP independent risk factors.	No differencies according to race	moderate
Maasomi, 2018, USA	Register-data base	PPCM=568 controls=1247 35	Incidence 1/2187 (0.05%) 75% readmission in the first 10 days pp. Late onset PPCM more common after PE/E and GIH and preterm labor. In-hospital mortality 1.2%	no significant diff in term or late PPCM. More ECHO in PE/E to find them earlier?	moderate
Mebazaa, 2017, South Africa	Prospective laboratory	PPCM=83 AHF=65	High PLGF or low s-flt-1/PlGf may be used for diagnosis.	AHF in non-pregnant individuals served for comparison!!	low

		control(delivery)=30 non-pregn=29	BNP much higher in PPCM than in normal pregnancy		
Ntusi, 2015, South Africa	prospective longitudinal	PPCM=36 AHF=53	PPCM more postpartum AHF 85 % ap Riskfactors PPCM twin, smoking, cardiomegaly,left atrial hyperplasi left bundle branch block etc AHF left ventricular hypertrophy	5 deaths in PPCM, none during AHF	moderate
Sagy, 2017, Israel	Register-data base	PPCM=42 controls=160 964	Higher uric acid in PPCM OR1.34 (95%CI!.003-1.778) Incidence PPCM 1/3832 (0.03%) Uric acid mg/dl 4.7(1.3) vs 5.3(1.4) p<0.002	low absolute uric acid levels	low
Sarojini 2013, India	case-control	PPCM=46 controls=40	C-reactiveprotein 08 22(1-90)<0.05 IL-6 31.52(8.83) 77.19(34.4) <0.005 TNFalfa 3.2 9.6 (0.2-20.0)<0.001 predictor death; NYHAFCIV, IL6 and TNFalfa	small number of patients uncertainty of figures no power	low
Umazume, 2018, Japan	prospective case-control	Hypertensive diiseaes n=24 controls=51	ROC troponin I predicting poor LV relaxation 0.82 and 0.81 respectively	no power analyses small number of patients	low
Vaught AJ, 2018, USA	prospective case-control	63 PE 36 controls	PE changes in right and left side of the heart, mostly diastolic impairment. BNP was not suitable in this study	no power but Bonferroni use	low

13. Blodanalyser

Outcome variable: Blodanalyser

Author year country	Study design	patients, n	Results	Comments	Quality
Multiple variables					
Cantu, 2014, USA	Multi-center randomized double-masked	GH=2752	Composite outcome compared to mild PH, aOR Median(interquartile range) **I vs II** PTB <37 weeks 2.1(1.1, 4.0) PTB < 32 seeks	**Pregnancy induced hypertension** Composite neonatal outcome Fetal or IUFD Baseline difficult to understand: there is	Moderate

			Plac abr 7.1(1.9, 27.5) Cesarean 2.1(1.3, 3.2) SGA NS NICU NS Comparison **III vs IV** Composite neonatal 2.5(1.3, 4.9) PTB, indicated PTB, and NICU significant higher frequency in IV **III vs I** **IV vs I** 3.6(2.8, 4.6) 7.8(5.0, 12.1) 3.8(2.8-4.6) 24.7(9.9, 61.8) NS NS 1.2(1.0, 1.5) 2.1(1.2, 3.0) 1.5/1.0, 2.0) NS 1.9(1.5,2.3) 3.9(2.5, 5.9) morbidity	differencies in age, BMI, race, smoker, heredity, education **I** mild PH, **II** mild PH+lab, **III** PH clin sign **IV** severe PH +lab II Imild/severPH +severe clin sign IV mild/severePH +lab+severe clin sign Platelets, ASAT, creatinine, LDH, bilirubin Blood smear Secondary analysis VIP trial	

Cordina M, 2015, UK	Retrospective case-control	PE=497 controls=497	**PE** No correlation between Hb and crea, ASAT or platelets Inverse correlation between Hb and birth weight =0.009 SGA or LGA Inverse corr to platelets </>2.5 percentile No verified recommendation on HB as predictor.	Gestational weeks 27-29 Singletons Hb, creatinine, platelets, ASAT 5-10% lower Hb in black race included 8 studies presented increased frequency of PE at high levels of Hb	low

Khalil, 2014, Saudia Arabia	Prospective Observational	Late SPE =30 mild PE=30 GH=30 Gestational proteinuria=30	Cut off sPLG (124.6 pg/ml) uPLG (13.3 pg/ml) urate (284 µmol/L) LDH (208 U/L) Dipstick (2+) 24h proteinuria (0.6g) ROC curves sPE against all other groups N=30 Sens spec PPV NPV sPLG 100 86.7 65.2 100 % 24 h proteinuria 76.6 84.2 54.7 93.5 dipst 100 64.1 41.1 100 urate 100 55 43.8 100 LDH 83.3 73.3 43.8 94.6 uPLG 100 74.2 49.2 100 AUC (95%CI) 93.5(89.7- 97.4)	Between 34-<38 gw sPLGF, uPLGF, Urate, LDH, DIPSTICK proteinuria, 24H proteinuria creatinine, ALT, AST, platelets, Hb, hematocrite Hb hematocrit no differencies crea, ASAT ALAT no differencies PLATELETS diff p <0.001 Unclear why this variable is missing in analyses.	low

			90.4(85.4-95.4) 82.2(73.2-91.2) 85.8(79.9-91.7) <80		
So J, 2016 USA	Retrospective chart review	n=481	Abnormal coagulation n=22(4.6%) Bivariate analys Clinical symptom/abn coag RUQ pain or tenderness 18.52 gestational age >/= 37 3.02 **RUQ and abnorm coag** Sens% spec PPV NPV ROC	Platelets, ASAT, ALAT, LDH, creatinine	low

			22.7 95.2 18.5 96.3 0.59		
Proteinuria					
Baba, 2015, Japan	Prospective observational	n=1033	Negative dipstick n=877 SPIP present Negative n=77 8.8% 1+ n=201 21.5% 2+ n=200 79.4% 3+ n=147 98.7% SPIP absent n=800 SPIP absent n=733 SPIP n=52 SPIP n=2	Significant proteinuria SPIP compared to dipstick False positive increased with increasing creatinine	high

Bramham, 2013, UK	RCT	PE 60+161 GH=110 CH=615	**Maternal outcome** N 60 161 PE <500mg >500mg SPE,% 26.7 34.8 ICU,% 1.7 2.5 Crea >90 mmol/l, % 7.1 18.4 **Perinat oc,** RR(95%CI) Premat < w 34 2.41(1.56-3.89) % <500mg >500mg Death 3.3 2.5 RDS 8.3 18.9 SGA 40.0 52.5 n= 615 110 **CH** **GH** SPE 5.9 10.0 ICU 0.5 0.9 Crea >90 mmol/l, % 3.4 7.5 Perinatal oc Death 3.4 0.0 RDS 2.9 0.0	Proteinuria 300-499 mg/24h and >500 mg/24h Secondary analysis of RCT for Vitamins in preeclampsia – trial(VIP) No control group!	moderate

			SGA 20.1 25.7		
Brown RA, 2013, UK	Retrospective observational	n=264	Proteinuria > 3 g/24 = 264 pulmonary emboli 2**(0.8%)** vs 70(**0.08%)** controls IUFD 11(4%) Very low birth weight(<1500g) 76(29%) Delivery <37 198/76%) <34 146(56%) <28 39(15%) cohort controls 2000-11 n= 81165 482(0.6%) IUFD 1140(1.4%)<1500g 3253(3.8%) <v37 3044(3.8%) <v34 845(1%) <28	Maternal and fetal morbidity in relation to different levels of proteinuria, ap and pp. To follow up and thromboprophylaxis	low

Kayatas, 2013, Turkey	Prospective Observational	suspected PE=200	PE n=127 24h mg P/C sens spec 300 0.28 60.4 77.8 2000 0.77 96.8 98.6 ROC mg AUC 95%CI >300 0.74 0.66-0.80 >2000 0.99 0.95-0.99 PPV NPV PLR NLR 77.5 60.9 2.72 0.51 96.8 98.6 6.97 0.03 Corr P/C and 24 h r= 0.828 p<0.0001	Proteinuria 24 h, Creatinine Ratio protein/creatinine Low correlations 24h at 0.3g increasing at increasing levels of proteinuria	low

Mateus, 2017, USA	secondary analyses of multicenter prospective cohort study	non-PE=102 mild proteinuria =258 massive proteinuria =36	Composite maternal morbidity was similar across the groups Composite adverse neonatal outcomes were significantly higher in the massive proteinuria PE compared with the other groups (p . 0.001	maternal and fetal outcome at >or>5g/24 h.	moderate
Payne 2011 Canada	multiple cohort study	n=2002	antenatal proteinuria level of proteinuria could not predict adverse events	proteinuria dipstick prot/crea and 24 h collection	moderate

Vaugh, 2017, UK	HTA-analyses		Evidence from this clinical study does not support the recommendation of 24-hour urine sample collection in hypertensive pregnant women. The SACR test had better diagnostic performance when predicting severe pre-eclampsia. All four tests could potentially be used as rule-out tests for the NICE definition of severe PE.	comparison of protein/crea and alb/crea	high
Uric acid					
Bellomo 2011 Italy	prospec-tive observa-tional	GIH =90 PE =73	**GIH** HB 112±13 platelet counts 216 ± 51 crea 63.3 ± 7.8 proteinuria 202 ± 19 uric acid 232± 48 umol/L	**log** regression PE uric acid per 59.48 umol/L OR 7.08 (3.20-15.69) p<0.001	low

			PE **p** 118 ± 11 O.002 170 ± 48 <0.001 78.1 ± 18.9 <0.001 190 ± 23 0.18 393 ± 77 <0.001	threshold value urate 309 log regression SGA OR1.58 (1.06-2.57) p>0.02	
Chen Q, 2016, China	1)retro-spective and 2)pro-spec-tive cohort study	1) PE=877 normotensives=580 2)PE=78 normo-tensives=5478	1)s-uric acid FGR+PE 421(138-673) PE 365(117-710) p=0.001 Mild PE 363(117-698 SPE 389(180-710) p=0.0018 Late 363 (117-698) Early 399(166-710) p=0.001 No predictive value I and II trimester III trimester significant increased uric acid compared with normotensives	S-uric acid decreased excretion of uric acid due to renal impairment	Low

Livingstone 2014 Canada	PIERs study	PE=1505	Uric acid predicts perinatal but not maternal adverse outcome tables see appendix no controls	uric acid PE maternal adverse perinatal adverse	moderate
Niraula 2017 Nepal	Prospect ive case- control	PE=51 normal pregnancy =51	Cystatin-C better than uric acid see appendix matched to age and gestational week	Cystatin-C, uric acid gw 24-36	low
Biomarkers heart					

Bozkurf, 2015, Turkey	Observa-tional	PE= 42 eclampsia= 16 normal n= 108	Troponin I control 0.0134 ± 0.0091 preeclampsi 0.017 ± 0.0085, NS control eclampsia 0.180 ± 0.136. p = 0.016 control, p = 0.014 preeclampsia D-dimer preeclampsia 1426 ± 430 ng/ml, eclampsia 2067 ± 580 ng/ml control 634 ± 228 ng/ml, p = 0.034 PE/control, p = 0.020 eclampsia/control	troponin, D-dimer	low
Umazume, 2018, Japan	prospec-tive	HP=24 NP=51	comparison with ECHO results:Troponin I corr till LV relaxation and increased Troponin, BNP and pro-BNP in HT pregnancy		low

Fayers, 2013, South Africa	prospec-tive observa-tional	PE=52 normal=63 primipara	**BNP pg/mol** preeclamptic 23.8(2-184) 15.0(1.8-206.4) 4.2(1.7-51.4) normotensives 6.0(0.5-45.2) 8.7(1.9-24.8) 5.95(2.2-38.7)	gw 28-40, intrapartum, to 1-7 days pp see table appendix elevated tissue Doppler estimations of LV filling pressure.	low
Millman (PIERs) 2011 Canada	subgroup analysis PIERS	adverse =201 normal=1333 women with PE	POX <93% predict maternal but not perinatal adverse events see appendix	SpO2= POX adverse events	moderate

Liver function					
Breslin E 2013 UK	Retro-spective cohort	n=925	1st quintile 0-0.21 mg/L n=157 adjOR(95%CI) CS fetal distress 2.25(1.27-5.61) poor mat oc 3.12(1.2-5.72) poor inf oc 2.5(1.25-5.19 Adjusted for age, BMI, ethnicity, age at delivery, sBT dBT	Bilirubin(**low**) Maternal and fetal morbidity Reference third quintile Low sensitivity	low
Dacaj, 2016, Bosnien-Herzgo-vina	prospec-tive case control	PE+IUGR= 60 PE+non-IUGR=60	IUGR AST 27(22-34) ALT 20.5(15-2.8) LDH 509(297-796) bilirubin14(13-15) cholesterol 6,4(5.7-7.4)	AST,ALT,LDH, bilirubin,cholesterol association SGA AST,ALT,LDH cholesterol	low

			non-IUGR p 14(11-19) <0.001 11.5(10-13) 0.001 357(300-456) <0.001 13(11-15) 0.052 5.5(4.7-6.3) <0.001		
Kozic(PIERS) 2011 Canada	prospect ive multicen ter cohort	PE abnormal tests=1056 normal tests=952	Increased AST,ALAT LDH and S-albumin related to adverse events see appendix controls normal values for pregnancy	after w 20 AST, ALT, LDH, INR, total bilirubin ,S-albumin	moderate

Suresh 2017 India	prospect ive cohort	pathologic liver tests=197	INR and S-total bilirubin predictive for maternal and fetal outcome S-bilirubin better than INR see appendix 3 no controls	AST, ALT , INR, bilirubin, Hb, platelets unknown start blood sampling until 8 weeks pp	moderate
Hemostasis					
Gauzevoort 2007 the Nether- lands	cohort	n=216	PE severe EO hereditary trombofilia no effect on maternal disease but on IUGR.	trombofili-PE	low

Heilmann 2007, Germany	prospec-tive case control	PE =EO 50 PE =LO 61 normal = 33	EO increased thrombin generation high levels of D-dimer and decreased antithrombin in comparison with LO controls	Coagulation D-dimer	moderate
Pinheiro 2012	SR meta analysis	PE=NA controls=NA	Higher levels of D-dimers in PE see appendix 3	D-dimers	low
Morikawa, 2019, Japan	retrospec-tive analyses	PE=94	preeclampsia time to delivery 94(3.2%) PE >78% AT may be used as predictor of delivery in 7 days.	antithrombin plasma and ascites	

Marietta 2007 Italy	Prospec consequ tive observat ional	PE=73	decrease in fibrinogen, platelets antithrombin prognostic value of antithrombin no controls see appendix	antithrombin, fibrinogen,platelet counts	low
Ogawa M, 2014 Japan	Retrospe ctive chart study 2003- 2010	PE=106 PIH=33	PE correlation AT/S-albumin 0.343 p 0.003 AT/TP 0.366 p 0.001 PIH correlation 0.504 p 0.003 0.619 p 0.001	Antithromin, **serum-albumin**, total protein (TP). PE=preeclampsi, PIH= pregnancy induced hypertension	low
Weenik 1983, The Netherlands	prospect ive study	653 women	No depression at chron HT but at GH and PE	Antithrombin	moderate

Weenik 1983, The Netherlands	prospect ive study	653 women	AT depression in pre-eclampsia is caused by increased consumption. AT I11 levels correlate with maternal morbidity as revealed by hepatorenal damage.	Antithrombin	moderate
Samejima T, 2019, Japan	retrospe c	PE=53 GH=37	Hypertensive pregnancy Preoperative values; S-albumin, decreased AT and heavy proteinuria risk factors for acute kidney injury.	Antithrombin s-albumin urine protein/creatinine ratio	low
Weiner, 1988, USA	Prospec-tive observa-tional	PE=36 GH=2 Eclampsia= 1	AT delivery n=47 correlation AT vs platelet count 0.53 p<0.005 correlation AT vs FPA -0.29p<0.05	Antithrombin platelets	low

Weiner, 1990, USA	diagnos-tic	renal biopsy n=12	PE, renal disease, specific picture at PE and renal diseases, some the latter though suspected PE		low
Laskin S, 2011, USA	Prospect ive study part of PIERS-study	abnormal coagulation =105 normal coagulation =1300	**Abnormal coagulation** Age 30(26-34) Corticosteroids 46(43.8) $MgSO_4$ 55(52.4) Gestational inclusion <34 weeks 59(56.2) Gestational age delivery 33.6(30.6-36.9) **Platelet count <50 x10^9/L , n=27** n(%) OR Abn coag 9(33.3) 7.78 (3.36-18.04) Adv mat 15(55.5) 11.32 (5.19-24.68) Blood 12(44.4) 25.27 (10.92-58.47)	Relation platelet and INR and fibrinogen Abnormal coagulation INR >1.06 Fibrinogen<3.54 g/L Relation abnormal coagulation and adverse events as blood transfusion And maternal composite adverse outcome Placenta ablation NS	moderate

			p<0.05 all calculations above **Platelets 50-99 x10^9/L n=95** n(%) OR 14(14.7) 2.69 (1.44-5.02) 9(9.5) 2.21(1.35-3.58) 7(7.4) 2.5(1.08-5.87) **Platelets <100 x10^9/L** % Sens spec Abn coag 21.9 92.4 Adv mat 15.8 92.2 Blood 31.7 92.3 Abnorm coagulation Adv mat 15.1 93.5 Blood 21.7 93.2 **Platelets 100-149 x10^9/L** Abn coag 21.7 % OR 1.30(0.78-2.17) Adv mat 26 1.29(0.90-1.85 Blood 10 1.20(0.58-2.48)	(>100 platelets NS) **Normal platelet counts will not rule out abnormal coagulation** EDA hos 89 % av 122 women with platelets <100 no complications (too small number to draw conclusions)	

			37.0(34.5-38.7) P<0.001 platelets < 100 x10^9/L PPV NPV 18.8 93.6 abnormal coagulation 19.7 90.0 maternal advents 15.6 96.8 blood transfusion		
Marchetti, 2015, France	case-control	PE severe=143 PE mild=199 normal=195	anti beta2GPI antibodies and LA associated with severe PE but not with mild. see tables appendix controls	Antiphodpholipid antibodies after PE 6 months after delivery	moderate

Spiezia L, 2015, Italy	Case control study	PE=90 normal=60	**PE n=30** **ROTEM** EXTEM CFT,s 62(15) Alpha angle 78(4) MCF,mm 72(5) Lys,% 2(3) INTEM MCF,mm 71(4) Lys,% 2(3) NATEM MCF,mm 64(6) Lys% 1(3) **Normal pregnancy n=60** 76(14) p<0.001 75(4) p=0.002 66(4) p=0.001 11(5) p=0.001 65(5) p=0.001 11(4) p=0.001 61(4) p=0.001 11(4) p=0.001	Overlap PE controls all variables Larger prospective studies needed None platelets <100 x10^9/L	low

Zheng, 2015, USA	Narrative review	NA	<10% ADAMTs13 hereditary >20 % acquired deficiency treatment plasma, plasma exchange, ADAMTS13 concentrate		moderate
s-Flt ,PLGF					
Lehnen H, 2013, Germany	Retrospective study	175 PE n=63 PIH n= 34 Proteinuria n=6 normal=72	Cut off ratio: 85 % sens spec PPV PE 59.38 93.62 86.36 PIH/PE 5.88 40.63 5.00 Prot/PE 0.00 91.62 0 EOPE 62.50 100 100 LOPIH 0.00 93.33 0 NPV OR p 77.19 1.034 <0.0001	sFlt-1/PLGF, ratio **Conclusion**: ratio not appropriate for prediction of PE Indicator IUGR at EOPE	low

			44.83 0.98 0.0003 76.47 0.88 0.024 40 1.03 <0.0001 72.4 1.016 0.039		

14. Prediktion andra trimester
Outcometabell

ANDRA TRIMESTERN FÖRSTA SÖKNINGEN

Afshani N,2013,USA	Syst review- Medline, EMBASE, Cochrane 12 articles Kaaja 1999 n=9, Borghi 2000, n=40, Folk 2005 n= 7, Kale 2005 n=40, Resnik 2005 n=34, Tithonen 2007 n=19, Rafik 2009 n=35, Fustaret 2010 n=20, Moghbeli 2010 n=63, Speksnijder 2010 n=22, Tanuous 2010 n=6	12 observational studies (11 pro, 1 retro) 2 high quality PE pat (6-63) Rafik 2009 n=35, Tanuous 2010 n=6 (321-22-12)	Excluded well defined	proBNP and PE and heartcompl Modified cochrane review for diagnostic tests and study quality OR 30,7 Rafik n=35 (95% CI 3,8-291) OR 21 tihtonen n=19 (95% CI0.5-192)		2 studies no change in pro BNP 4 studeies hight proBNP in PE 1 study no diff norm/PE 7 of 8 studies high in PE 1 study BNP; PE>HT 5 studies high BNP-more complications FÖR TREDJE TRIM, ENDAST TVÅ STUDIER HAR MED SECOND TRIM, MEN EJ ANALYSERATS SEPARAT.	+	+	+	HIGH
Akkermanns J 2014, Netherlands	Prosp. cohort PETRA	I=216 PE C=2023	Not defined	2^{nd} 3^{rd} trim severe early PE 24-34w, External validation of fullPIERS model and adverse outcome within 48 h. gest age, Chest pain or dyspnea, spO2, TPK, S-krea, ASAT predictor variables: worst values within 48. Without adverse outcome=143 Adverse outcome=73 Adverse outcome within 48h; PPV 70.7%, NPV 98,3% auc roc 0.97 CI 95% (0.87-0.99), within 7 day; PPV	No validation cohort	Basic characteristics the same No validation cohort Small Retropective adding of data were laboratory values taken within 2 weeks upto 12 h after inclusion. In the study group half of the women (111) had received plasma expansion and the other half not.(105) FLYTTA TILL KOMPLIKATIONER. DUBBELT, REDAN MED	?	-	?	LOW

				32,2%, NPV 85,7%auc roc 0.80 CI 95'% (0.70-0.87)						
Alvarez-Fernandez, 2015, Spain	Case-control retrospective	N=257 susp.PE <34w=62, PE 25 >34w= 195,PE 49 1st, 2nd, 3rd trim	N=24	Pediction for developing PE. Vit D + sflt(PlGF ratio in ePE and lPE. >34w; 25OH D vitamin < 50 nmol/l OR 4.6 (1.4-15) sFlt/PlGF > 45: **OR 12** 95% CI (5.0-27) for PE <34w, 25OH d vit no assoc, sFlt/PlGF >23**: OR 58** CI95% (11-312),	<34w no PE 32 >34w no PE 146	Controls developed no PE. Results significant for 2nd and 3rd trim. Low 25OH D levels significant for >34w. 1st trim samples too few Excluded pat not defined Cut off levels for sFlt/PlGF taken from own early small study Studypop:multiple gest and IUGR more common I PE groups PROVER TAGNA VID KLINISK PRESENTATION. D-VIT ÄV TAGET äv 1:st trim, STEFAN HAR MED TILL 1:st TRIM	?	?	-	LOW
Alpoim P, 2013, Brazil	Systemic Review	2 studies in review 992 PE, 883 cntrls		Blood groups and PE	AB associated w PE Increased vWF and factor VIII	ÄR med i 1st trim, ev till riskfaktorgruppen? Stefan har med	? / +	?	+	MEDIUM/LOW
Arisoy R 2016 Turkey	Prospective cohort	N=157 I=77 PE, C=180	Exclusion criteria defined but not numbers	Late 2nd and 3rd trim. Vit D: 25(OH)D Levels<20ng/mL a 12.45 OR (1.66-93.18) for severe PE		Small group of patients	+	?	?	LOW
Acestor, N. 2016 Clin Chem Lab Med	Systematic review	135 studies on biomarkers :49 blood, 9 urine		Blood and urine markers in low resource setting (2008-2013) 1st, 2nd 3rd	Good blood: s-Flt1, sEng, GlynFN, PlGF, sUric acid Good urine: Congophilia red, adipsin	INKLUDERAD: SVÅRT ATT AVGÖRA TRIM OCH SENS OCH SPEC FÖR ETT FLERTAL MARKÖRER				

Aghajafari, F, 2013, BMJ	Systematic and meta	31 studies		25(OH)D levels and pregnancy outcome <75nmol/L and <37,5nmol/L	Low levels associated w bacterial vaginosis, SGA, increased PE, GD Insufficient serum levels of 25-OHD Pooled OR pre-eclampsia (1.79, 1.25 to 2.58), and small for gestational age infants (1.85, 1.52 to 2.26).	EJ PREDIKTIONSMODELL; SVÅRT ATT AVGÖRA TRIMESTER.				
Al-Rubaie, ZTA 2016 BJOG	Systematic review	29 studies, 70 models (22 simple models)		Performance of models		Parity, PE history, race, CH, conception methods AUC 0,76 (0,67-0,90) Good table ÄR 1:a trim, inkluderad men de har ej funnit artikel	+	+	+	HIGH
Asvold B, 2014, Acta Obstet, Gyn Scand	Nested-case-control	(35940) 121 preterm, 158 preterm PE, 356 controls	'exclusion critera and excluded pat well defined	HCG and PlGF in each trimester	High HCG in 1st trimester associated with LOW risk preterm PE High HCG in 2nd-3rd trimester associated with preterm PE (OR 4-4,8) +low PlGF in 2nd OR 36,9 S-HCG above median in 2nd trim and PlGF below median , riks preterm PE OR 36.9(8.2-165.9) S-HVG and sFlt above median risk preterm PE OR 5.7 (2.6-12.4)	Bara OR	+	?	+	MEDIUM

Bredaki FE Ultrasound Obstet Gynecol, 2016 UK	Prospective Case-ctrl	17071 (488PE) cases in 11-13gw, 8583 (217PE) in 19-24, 8609 (208) in 30-34 gw	Exclusion definied	Serum alpha-fetoprotein Prospective screening 5-fold validation AFP increased up till -24 gw in PE Maternal factors improved		excluded from 1st trim to 2nd and 3rd trimester is 50% lower-ie selektionbias Inkluderas, med i andra sökning	+	-/?	+/?	LOW
Burris HH 2014 USA	Prosp cohort Vit D PE	2128 1591 56PE 109 GH	Exlusion defined	I=PE C=GH C2=non HT NS		Vit D level <10 gw ÄR v16-37, Ors, ej prediktionsmodell	+	?	+	MEDIUM
Chappell LC 2013 UK	Case control prospective multicenter	N=625 I; PE 346	Exclusion clearly shown	Predicition for PE with PlGF suspicion of PE, 2nd and 3rd trim <35w low PlGF; sens 0.96 CI 95% (0.89-0.99), NPV 0.98 (0.93-0.995), Spec 0.55 (0.48-0.61) low PlGF auc 0.87 (0.58-0.56) prediction of PE in 14 days	I: low PlGF C: normal PlGF	More complicated patients I n early PE group than in later. Otherwise baseline data similar I TREDJE TRIMESTERN	+	+	?	MEDIUM
Cohen JM. 2015 Plos ONE	Systematic and meta	64 studies		Antioxidant levels and PE		Not conclusive INKLUDERAD DOCK OKLART OM SKALL VARA MED. STEFAN HAR MED TVEKSAMT.				
Diguisto C 2013 France	Case control prospect	N=235 PE 56 Control 177	Exclusion criteria OK but no numbers mentioned	2nd trim I=PE C= no PE 2nd trim US + sampling. (PlGF/sFlt, Eng, lipidmark, Doppler notch). High risk population PE (23,8%), 27,8% severe, 5,9% < w34, PE had higher UtPI, bilat notch, lower		Small population Control group adequate Excluded not shown INKLUDERAD	. +	?	?	LOW

				PlGF, higher Triglyc higher leptin, Screening for PE AUC 0.795.						
Dogan E, 2014, Turkey	Case control prosp	C=80 I=80 PE ,early PE 37+late PE 43,	Not defined	s-VCAM-1 and fibronectin correlation in early and late PE 2nd 3rd trim Increased evels o fibronection and sVCAM in PE		High risk for selection bias HITTAR EJ, VARA MED?	-	+	?	LOW
Dogan K, 2015, , Turkey	Case control retrosp	N=284 I=severe PE 70 mild PE 49 C= 165	Not defined	TPK can predict risk for PE 2nd trim Severe and mild had different platelet count, and platelet volume and o platelet distr. volume		PROVER TAGNA I SAMBAND MED DIAGNOS TREDJE TRIM?	+?	?	?	LOW
EngelsT, 2013 Germany	Case control	338 : 232 cntrls, 64 PE, 42 CH/PIH		sFlt/PlGF >24 gw	ROC for sFlt1/PlGF (AUC all PE: ratio 96.4%, sFlt1 92.8%, PlGF 92.4%, supPE: ratio 93.6%, mPE: ratio 94.8%, sevPE: ratio 99.4%, HELLP: ratio 98.6%, each versus controls PIH and GP showed significant differences compared to controls ($p \leq 0.01$, respectively), mPE ($p \leq 0.007$), sevPE ($p < 0.001$) and HELLP syndrome ($p \leq 0.003$).	Ratio can differentiate among PE subgroups PROVER TAGNA VID DIAGNOS; EXKLUDERAS?	+	?	?	LOW

Forest J, 2014, Canada	Nested case control prosp	7929, 111 PE and 69 GH and 338 controls	Not well difined	sFLT-1 /PlGF ratio to predict early and severe PE measured in 20-32 gw AUC 0,977, 77,8%sens, 88,9% spec at 5% FPR		INKLUDERAD	+	?	+	MEDIUM
Gallo DM, 2016, UK	Prospective screening, 3 hospitals	123406		Chacteristics+Ut-PI, MAP, PlGF, sFLT1 High DR for early PE Link to free risk estimation AJOG website		Very high rate of excluded data for some of the analysis- , one mariker analyzed in less tha 10% of study cases INKLUDERAD	?	?	-	LOW
Gallo DM, 2013, UK	Prospective screening	50490 1442 PE	Exklusion defiened	Characteristics+Ut-PI, at 20-24 gw (transvaginal) In normal preg PI is affected by maternal characteristics (Afro-Caribbean) and in PE PI MoM to severity, particularly w SGA.		INKLUDERAD?		+	?	MEDIUM
Gallo D Fetal Diagnosis & Therapy, 2014 UK		17383: 70 early PE, 143 preterm PE, 537 total PE	Exluded defined	MAP measured 2 11-13 and w 20-24. best PR if measured at both time points DR 52,9 and 52, 9, both 60,0 at 5% FPR or 84,3 at 10% FPR		INKLUDERAD		+	+	HIGH
Gallos ID 2013 UK	Meta-analys Systematic Review	24 case-controls I=2720 women PE 5 cohort a 3147 (2^{nd} trim)	Excluded studies defined	24 studies; -WMD 0.78mmol/L (0.6-0.96) 5 cohort WMD 0.24mmol/L (0.13-0.34) Hypertriglyceridaemia, +second trimester preceding onset PE has higher WMD- weighted mean differences		Overall quality good Half of its case control RAPPORTERAR WEIGHTED MEAN DIFFERENCE		+	+/?	MEDIUM/HIGH?
Garcia B	RCT multicenter	11667, early onset 48, IUGR in 722,	Excluded well defined,	Doppler in second trimester 60% detected in an		INKLUDERAD	+	+	+	HIGH

Ultrasound Obstet & Gyn, 2016		early onset IUGR 93, early PE+IUGR 32		unselected population but did not improve outcome						
Kafkasli A, 2013J .Mat Fet and neonat Med	Retrospective	N= 406 259 PE 168 mild 91 severe	Excluded due to lack of data about 40%!	Role of Doppler UtA+maternal characteristics, ASAT, ALAT, LD and platelets Doppler predictor of prematurity OR 3.3 (1.7-6.4) Severe PE predictor of bad outcome OR 4.1 (1.9-8.9)		TILL KOMPLIKATIONER	-	?	?	LOW
Khalil A, 2016, Ultrasound Obstet Gynecol, UK	Prosp case control	C=172 GH=18 ePE= 22 lPE =22		1^{st}, 2^{nd},3^{rd} trim s-Flt, PlGF , sFLT/PlGF ratio, taken every 4^{th} w until delivery from w 11-13. sFLT/PlGF ration 11-13w and 19-22w.	AUC PlGF 0.70 (0.54-0.87) w11-13, longfitudinal 0.79 (0.74-0.84), sFlt 0.58 (0.44-0.73), long 0.74 (0.69-0.80), sFlt/PlGF ratio 11-13w 0.73 (0.60-0.86) longitude 0.85 (0.80-0.89)	PlGF lower in ePE p<0.001, PlGF lower w13in term PE and from w 27 in GH group, sFLt higher in ePE than contr (p<0.001),sFLt/PlGF ratio higher ePE and increased from w 11, Small groups EXKLUDERAS; FÖR FÅ PE FALL	+	+	?	MEDIUM
Kleinrouweler, C.E. 2013 Ultrasound Obstet Gynecol	Individual patient meta-analysis	8 databases, 6708 nulliparous (302 PE)		The use of a second trimester Doppler (PI, _RI, notching	Blood pressure, BMI+ PI, _RI, notching gives AUC 0,85	INKLUDERAD	+	+	?	Medium
Kurt RK, 2015, Turkey	Case control	C=50 I=52PE	Not definied	Red cell distribution avd PE 2^{nd} 3^{rd} trim Red blood cell width related to Pe and severity		Prospective- likely but not clear VID DIAGNOS, relation till severity.	+	-	?	LOW
Lambert-Messerlian G, 2014,USA	Case control	N=503+1375 cohort I=98 PE C=620	Excluded defined	2nd trim screening- PAPP-A, PlGF, endoglin, inhibin,A s-VEGF-R, FLRG change during pregnancy in PE An association of PAPPa and PlGF witn all PE in 1^{st} trim and 2^{nd} trim sampling and		Two cohorts with exclusion due to missing data about 90% of cases-registerstudy INKLUDERAD	?	?	?	LOW

				elevation of inhibin A and endoglin in sever early PE,mild PE						
Leanos-Miranda A, 2013, Hypertension, Mexico	3groups, no control group	N=501 mildPE 122 severePE 261 sPE + Hellp/eclamspis 118	Not defined	Sflt/PlGF ration and urinary prolactin and sENG in Preeclampsia 2nd and 3rd uPRL higher in SPE + HELLP sPlGF higher in mPE than sPE and SPE + help sFLT PlGF ration higher SPE and >sPE + HELLP sEng higher in sPE and >sPE + hellp		Groups Differing in age, gest age, , smoking, gest age at sampling earlier in sPE and s PE and help FLYTTA TILL KOMPLIKATIONER	?	?	-	LOW
Lehnen H, 2013,Prenatal Clinicla assessment	Retrospective screening	2nd trim, 63PE, 34 PIH, 6 proteinurea, 72 controls		sFlt1/PlGF ratio in second trimester	Ratio >85 was only seen in 37 out of 63 cases, only useful in early as indicator of severity	EJ SOM PEDIKTION; BARA SOM INDIKATOR AV SEVERITY KOMPLIKATIONER				
Li N, 2014, Sweden	Case control retrospect	N=645 I=177 PE o GH	Not defined	Doppler at w 23-24 and adverse outcome PE, preterm<34, preterm < 37, cs, neonatal care, iufd, sga 2nd trim 45% showed high utPI but Umbilical flow patologic in 3,7%. UtPI correlated with PE but nor GH.	2nd trim	Some patiente were trated with ASA- not specified HITTAR INTE	?	-	-	LOW
Liu Y 2015 China	Meta-analys	20 studies, 838 PE, 6138 controls	Excluded studies well described	Metaanalys: s-Flt1/PlGF ratio AUC 0.88 (0.77-0.89) 22% false negative and 16% false positive	Included studies: Kim 2007, Stepan 2007, Diab 2008, sibai 2008, Vivo 2008, Kusanovic 2009, Molvarec 2010, Ohkuchi 2010, Sunderji 2010, Verloren 2010, Chen	Ingår studier från Asien och Afrika. oklart när prover tagits. Svårt att utläsa resultat. Som en overall analys? ÄR INKLUDERADI FIRST TRIMESTER SOM TEXT ALLA TRIMESTRAR		+	?	HIGH/medium

					2012, McElrath 20112, Lehnen 2013, Odibo 2013, Villa 2013, Hanita 2014, Park 2014, Doherty 2014, Moore 2014, Stubert 2014					
Lopez-Mendez MA 2013, Mexico	Case control	N=102 I=pe 65 C=norm 37	Excluded not defined	Abnormal Doppler in PE OR 2,93 (1,2-7,3), PPV 89,2%, NPV 88,6% UtPI OR 2,6 (1.01-6,68)in pe Notch OR 9,0 (1,127-71,887) Umb OR 30,63 (1,47-639,71)	2^{nd} 3rd	Hypertensive treatment in some of PE patients but not specified Both patients in second and third trimester- not specified which gest age UNDERSÖKNINGAR VID DIAGNOS. FFA TREDJE TRIM	-	-	?	LOW
Macdonald-Wallis C, 2015, UK	Prosp. Cohort 2 cohorts	Develop.cohort 12996; 12679 +317 Validat; 3005;2971+86PE	Excluded defined	Maternal charcter 1^{st} and MAP w 20-36 MAP form w28 improved predicition PE, preterm birth, SGAm maternal characteristics **Auc** maternal char + MAP1; 0,77 +MAP2 0,79 + gest age 36w0,88 1^{st}, 2^{nd} and 3^{rd} trim	1st2^{nd} 3rd	Incidence in validation too few, low power? INKLUDERAD ÄVEN TILL 3:E TRIM		+	?	MEDIUM/ HIGH
Madazli R, 2014, Turkey	Retrospect Case Contr	N=144 ePE 91 lPE 63 3rd	Not def	UtPI higher in ePE 71,4% vs 30,1% SGA, oligo,apgar neonat outcome higher in ePE than lPE	2^{nd} 3rd	Maternal characteristics not well defined https://link.springer.com/article/10.1007%2Fs00404-014-3176-x TILL KOMPLIKATIONER	+	-	-?	LOW
Mc Carthy FP 2015, Ireland	Retrosp analysis of a prospective cohort ALSPAC	12996 validated in 3005	Not def	1^{st} 2^{nd} 3^{rd} trim Early preg characteristics in first trimester gives AUC 0.79	No predictive value for SGA or PTB	Short study with no major problems. INKLUDERAD.		?	?	LOW

				(0.73-0.85) and 0.88 (0.84-0.93) at 36gw+MAP. Effect of **MAP makes a different first at 28gw for PE AUC 0.84 (0.79-0.86)**		HITTAR INTE; TAGIT IINFO FRÅN OUTCOME TABELL, EV TILL TREDJE OCKSÅ				
Metcalfe A 2014, Canada	Cohort	N=45287 Develop 22633 Validation 22654	defined	1st trim and 2nd trim samples: Serious perinatal events and PE in relation to biomarkers,;AFP, hCG,InhibinA, uE3 and characteristics AUC 0.78 for severe PE		Also stillbirth, HELLP, PTB as well as PE Predictive value of isolate markers low INKLUDERAD		+	?	MEDIUM
Stubert J, 2014, Germany	Retrosp cohort	N=68 EarlyPE= 44, latePE 24	Excluded not def	Difference early o late **severe PE** and predictors 2nd and 3rd trim		UtPI abnormal; increase risk low apgar OR 8.0 and preterm OR 17,9 SGA OR 4,9 TILL KOMPLIKATIONER HITTAR EJ FULLTEXT https://www.degruyter.com/view/j/jpme.2014.42.issue-5/jpm-2013-0285/jpm-2013-0285.xml	-	?	?	LOW
Tayyar A 2014 UK	Prosp screening	N=83615 normotensive 2140 PE but this study I=360 PE C=13878 normotensive	Not defined which were excluded from the primary cohort	MoM UtPI and maternal character at 30-33 gw could iidentify 90% of pregnencies developing PE-false pos rate of 5%		A first trim screening was also done+maternal characteristics Complete set for 350 PE and 13 878 cntrls PI higher in Afro-Carribean TILL TREDJE TRIM, DUBBELT; FINNS REDAN DÄR	+	-?	+?	**MEDIUM/**LOW
Tayyar A 2016 UK	Prosp cohort	w 11-13=7734 w19-24=31120	Not defined	MAP and maternal history 1st 2nd 3rd trim		INKLUDERAD	+	?	?	**LOW**

		w 30-344 29802 w 35-37 5543		12w: DR /FPR10%) PE delivery <32w =66% 12+22w:72%, Delivery 32-36+6: 12+22+32w screen; 54%, 56% 81%. >37w pedeliv; 12+22+32+36wscreen 45% 43%, 49%, 59%						
Wright A, 2016; UK	Cohort Case control	W 11-13=94989 W 19-24 7597 30-34w=8088	Not well defined	Maternap factors adn bHCG and PAPP-A DR maternal 45%, mat + PAPP-A 11-13w=51%, 30-34W 53% PAPP-A + bHCG + mat 19-24 55%, 30-34W 54%		Combination of maternal factors with PAPP A and beta HCG improved prediction EXKLUDERA DUBBEL	+/ ?	?	?	LOW/MEDIUM
Wright D, 2016, Ultrasound Obstetr gynecol, UK	Prosp cohort case control	19-24w C=7318 PE=247 30-34W C=8021 PE=243	Excluded not defined	For visits 19+,24+30+ and 34+6- Maternal factors and sFLT at 19-24w did not improve prediction; Matern+sFlt 30-34 DR 94% preerm PE and 54% term PE Maternal+sflt 30-34+19-24; improved DR preterm 99%, term Pe 64%.		in a large cohort sFlt was measure in some pat that are included, total population 123406 INKLUDERAD	+/ ?	?	?	LOW
Wright D, 2015, Am J Obstet Gynecol, UK	cohort	N=120492 Pe 2704 No Pe 117788 Risk 1st 2nd trim	Excluded defined	Prediction model by maternal characteristics where maternal age, increasing weigth, afro caribbean, South Asian, cronic hypertension, diabet es, SLE, APS, history PE o r in family, IVF pregn, Risk for Pe decreased with increasing height and if screen positive; detection rate 40% PE, 48% pe		Risk screening for PE by – medical history w 11-13 No validation cohort , therefore external validation, further studies needed FIRST TRIMESTER; FINNS MED DÄR, DUBBEL	+	+	+/ ?	HIGH

				deliver <37, 44% pe delivery <34.						
Wright D, 2016, Ultrasound Obstetr gynecol, UK	Prosp cohort case control	N=117710 no PE Early PE 790 Late PE 1958 GH 2948	Exclusion not clear	Two stage screening with MAP, and history 1st trim and ultralsound and PIGF in 2nd trim With 10% false positive UtPI w 11-14; Pre early onset: sens 47,8%(39,0-56,8), spec 92,1% (88,6-94,6), pred early IUGR: sens 39,2%, (26,3-53,8), spec 93,1%, (90,6-95,0), ane PE or IUGR; sens 26,4% (22,5-30,8), spec 93,3% (90,0-95,1))	Detectionrate MAP, UtPI, Plgf; 74%, 2 stage screen MAP maternal first and utPI plgf second; detec rate 71% with 50% less examinated. Screen at 19-24w: det rate MAP, maternal UtPI plgf; 84%, 2 stage det rate only 70%. If 30% was offered screen and and higher if 405 was offered	Very low numbers of patients undergping measurement with Plgf and varying sizes o grupps amalyzed INKLUDERAD	+/?	?	?	LOW/MEDIUM
Zeisler H, 2016, Multicenter	Prospective multicenter	500 development cohort 550 validation 101+98 PE		sFlt/PlGF ration to predict PE after 1 and 4 weeks	Cutoff value of 38 <38 negative predictive value within a week 99.3% 80%sens, 78,3% spec >38 positive predictive value within 4 weeks 36,7% at 66% sens and 83,1 spec		+	+	+/?	HIGH

ANDRA TRIMESTERN ANDRA SÖKNINGEN

Agrawal, S., et al. (2018). Hypertension **71**(2): 306-316 Several countries, all continents	Systematic review and meta analysis for sFlt/PlGF	15 studies, 18 groups when divided on outcome early/late PE. 534 PE,	No dropouts after specified inclus	Overall: sens 80% 0.68-0.88), spec 92% (0.87-0.96). High risk group: sens 85% (0.66-0.94), spec 87% (0.76-0.93), low risk group sens 77% (0.61-0.88), spec 94% (0.88-0.97).	Kliniskt applicerbar	19-37 gw, prediction of preeclampsia, both early and late onset. Heterogeneity in studies. Andra och tredje trimester, prediktion av senare preeklampsidiagnos				

FINNS ÄVEN I TREDJE TRIMESTER AS	ratio in predicting onset of preeclampsia	19587 controls	ion criteria (originally 3736 studies)			Hög specificitet men frågan är vad den naturliga negativa prediktiva värdet för preeklampsi är utan test så sent i graviditeten om man ännu ej fått preeklampsi. Skulle det förändra svensk handläggning? Isåfall mer rule in än rule out?				
Andersen, L. B., et al. (2016). Hypertens Pregnancy 35(3): 405-419 Denmark AS FINNS ÄVEN I FÖRSTA TRIMESTER	Prospective cohort	6707 were offered inclusion and 2874 (42.9%) enrolled A total of 1909 blood samples were available.		Concentrations of sFlt-1, PlGF, and sFlt-1/PlGF in GW20-34 were predictive of PE development, but not in GW8-14. PlGF outperformed sFlt-1/PlGF ratio with an area under curve (AUC) of 0.755 vs. 0.704, p = 0.002. The highest AUC values for PlGF and sFlt-1/PlGF ratio were seen for severe early-onset PE (0.901 and 0.883). Negative predictive values were high for all PE types, but positive predictive values were low.	Kliniskt applicerbar. PlGF och Flt-1	First and second trimester screening for preeclampsia Relativ låg AUC för att fungera som ett single screeningtest. Bör även läggas till i tredje trim? AS				
Andrietti, S., et al. (2017). Ultrasound Obstet Gynecol 50(2): 221-227 United Kingdom AS	Prospective cohort	Complete data for biomarkers: 3663 healthy, 136 PE. Overall 123406 pregnancies		AUC:s for maternal risk factors, PlGF, UtAPI presented for first, second, third trimester for PE <37 weeks and >37 weeks. Also combinations of measurements in all 3 trimesters. Conclusion that a combination did not lead to	Kliniskt applicerbara markörer	Large cohort but for biomarkers smaller. Svårt att förstå hur de byggt modellen då de har 120000 graviditeter men sedan knappt 4000 kvinnor som har biomarkörer och de skriver att de använt simulering.				

FINNS ÄVEN I FÖRSTA OCH TREDJE TRIMESTER				higher AUC. See article for all numbers.						
Contro, E., et al. (2017). Mol Diagn Ther 21(2): 125-135. Countries not stated	Systematic review and etaanalysis	376 cases, 270 controls		First and second trimester screening with cell free fetal DNA for development of preeclampsia Four studies (82 cases and 1315 controls) evaluated cffDNA in early-onset PE, with DRs of 18 and 68.8% at 11–13 and 17–28 weeks, respectively, at a false positive rate of 10%. Nine studies (including two considered for early-onset PE) encompassing 376 cases and 1270 controls were available for the evaluation of 'any PE'. At 11–14 weeks no significant DR was found, while at 15–28 weeks the DR was 37%.	Ej kliniskt applicerbar markör	Second trimester screening. Promising to detect early onset PE in second trimester, not enough data for any PE. Ej gått vidare med pga ej kliniskt applicerbar markör.				
Erez, O., et al. (2017PLoS ONE 12(7): e0181468 United States AS FINNS ÄVEN I FÖRSTA TRIMESTER	Case control	90 patients with normal pregnancies and 76 patients with late-onset preeclampsia (diagnosed at _34 weeks of gestation).		After 22 weeks of gestation, PlGF was the best predictor of late-onset preeclampsia, identifying 1/3 to 1/2 of the patients destined to develop this syndrome (FPR = 20%) Oklar selection av kontroller, proteomics där de proteiner med störst skillnad (>10% mellan grupper) valdes ut för att konstruera AUC. Risk för	PlGF kliniskt applicerbar	Andra trimester screening PlGF PlGF bättre än kombination av biomarkörer i v. 22 men låg sens (30%) vid FPR 20% Bör även läggas till i tredje trim? AS				

				överestimering pga fall-kontroll design.						
Ferguson, K. K., et al. (2017). Am J Obstet Gynecol 216(5): 527.e521-527.e529 USA AS FINNS ÄVEN I FÖRSTA OCH TREDJE TRIMESTER	Prospective cohort	50 mothers who experienced preeclampsia and 391 mothers with normotensive pregnancies		At visit at 18 weeks; hazard ratios for a combination of 8-isoprostanel 8-hydroxydeoxyguanosine, C-reactive protein, the cytokines interleukin-1b, -6, and -10, and tumor necrosis factor-a showed an increased risk of preeclampsia with 1.31-1.83, in association with an interquartile range increase in biomarker. Hazard ratios at this time point were the most elevated for Creactive protein, for interleukin-1b, -6, and -10, and for the oxidative stress biomarker 8-isoprostane (hazard ratio, 1.68; 95% confidence interval 1.14-2.48). No predictor reached enough performance to be used clinically as predictor. No AUC curves or sens/spec were calculated. Nested case control design based on preterm birth – not reliable for prediction in a general population. Hypertensive pregnancies other than preeclampsia exluded – overestimation of results?	Inflammations och oxidative stressmarkörer för PE	urine and plasma samples at 4 time points during gestation (median, 10, 18, 26, and 35 weeks). Inflammatory profile elevated in women who later developed preeclampsia and was more pronounced in LOPE. Not good enough to use as a clinical prediction model. No AUC.				
Fouad Gomaa, M., et al. (2016). J	Prospective cohort	825 low risk primigravidas	53	C3 levels at 14-20 weeks gestation had a sens of 83.3% and a spec of 100% and NPV	C3 levels for prediction of preeclampsia.	Second trimester screening. Very low risk population but even so 10% developed				

Reprod Immunol 117: 4-9 Egypt AS	(though from Egypt – exclude?)			98.3% when the cut-off value was 53.1 mg/. For the mean RI, the best cut off value found was 0.72 with 100% sensitivity, 99.1% specificity, 92.3% PPV and 100% NPV. For the mean PI the best cut off value was 1.35 with 100% sensitivity, 94.1% specificity, 63.2% PPV and 100% NPV. The combination ofserum C3 level and mean uterine artery PI showed 100% sensitivity, 97.4% specificity, 80% PPV and 100%NPV in prediction of PE.		preeclampsia. Unexpected high values of AUC – ever replicated? C3 not clinically applicable but uterine artery doppler is.				
Anna										
Kwiatkowski, S., et al. (2016). Poland. **Finns även i 3 trimester**	**Case-control.**	**83 PE/of whom 42 eoPE, 41 loPE(>34 gw). 43 controls**		**eoPE andloPE and control (and IUGR). Statistically significant for PE groups D-dimer higher and APTT lower than in control group. S-Flt higher, PlGF lower, S-Flt-1/PlGF ratio higher, Il-6 and hsCRP higher I PE groups than controls.**	**Kliniskt applicerbar markör**	**Second and third trimester screening** **Exkludera** **Ingen screening, bara korrelationer mellan olika PE subtyper och nivåer av biomarkörer**				
Kwiatkowski, S., et al. (2017). Poland.	Case-control.	83 PE/of whom 42 eoPE, 41 loPE(>34 gw). 43 controls		Se results ovan. Fibronectin significantly higher in PE groups than control group. Correlations between S-Flt-1 and Fibronectin r=00.34, P< 0.001. Correlation between Fibronectin and PlGF: r0-0.28, P<0.01 for all PE, IUGR and controls.		Exkludera. Ingen screening, bara korrelationer mellan olika PE subtyper och nivåer av biomarkörer				

Kwiatkowski, S., et al. (2017). Poland. Finns även i 3 trimester	Case-control.	83 PE/of whom 42 eoPE, 41 loPE(>34 gw). 76 controls		S-Flt-1 and PlGF and S-Flt-1/PlGF ratio. Concentrations in different stages of pregnancy. Lower PlGF concentrations in eoPE than in loPE. Opposite in control group. In PE groups no differences in SFlt-1 concentrations. Increased concentration in the group of physiological pregnancies after 34 gw. SFlt-1/PlGF ratio values higher in eoPE than in loPE and in control group.	Kliniskt applicerbar markör	Second and third trimester screening Exkludera Ingen screening, bara korrelationer mellan olika PE subtyper och nivåer av biomarkörer
Kurtoglu, E., et al. (2016).Turkey. Finns även i 3 trimester	Case-control.	250/100 NT/121 sPE/29 mPE		Platelet count, mean platelet volume, platelet distribution,width, platelet crit. Samples at time of admission. Samles fronm normal pregnancies were taken at last antenatal visit prior to delivery. Mean platelet volume and platelet distribution width was significantly higher in PE group (p=0.006 and 0.046) Platelet count, mean platelet volume, platelet crit was increased in late onset PE (p<0.05)	Kliniskt applicerbar markör?	Second and third trimester screening? Exkludera. Ingen screening, bara korrelationer mellan markörer och sjd/frisk.
Litwinska, M., et al. (2017). U.K. **AS**	Prospective cohort study.	7748 singleton/ 268 (3.5%) developed PE		Inclusion at 19-24 weeks at routine US. Competing risk model for PE<gw32 and <36gw and ≥36 gw. High, intermediate and low risk groups. Cut of 1/100 for	Kliniskt applicerbar markör Är cut-off värden, ej AUC	Second trimester screening

		Maternal history, MAP, UtA-PI, PlGF, PAPP.A and b-hCG		PE<32 and 1/300 for PE<36, then proportion of the population stratified into high (0.9%)-, intermediate (17.2%)- and low risk (81.9%). High-risk group contained 97% of pregnancies with Pez 32gw, 45% of those with PE32-35 gw, Intermediate cgroup contained further 46% of women with PE at 32-35 gw. Low-risk contained 0.03% of PE <gw32 and 9% 32-35 gw.		
Leme Galvao, L. P., et al. (2016). Brazil. Finns även i 1 och 3 trimester	Case-control.	Case-control 456 (169 severe preeclampsia,287 controls)		High pregestational BMI aOR 2.77 (1.75-4.38), p<0.001, first gestation 1.85 (1.18-2.92) p<0.008, low level of consciousness on admission 3.31 (1.30-8.42) p=0.01,2 associated with severe PE in multivariable analyses. IL1B genotype were associated only in univariate analyses.	Kliniskt applicerbar markör	First, second, third trimester screening Case – control = överskattning av betydelse av riskfaktorer? Redan kända riskfaktorer som inte gjorts som prediktionsmodell – ej gå vidare med betygsättning?
Lei, J., et al. (2016).International/China. Finns även i 1 och 3 trimester	Meta-analys and own studies.	6 included studies of pregnant women. 301 PE/456 non gravida hypertension/344 controls.		Angiotensin II tpe 1 receptor autoantibody (AT1-AA) was associated with PE poopled OR 32.84, (95% CI 17.19-62.74) but weaker with non-pregnant hypertension pooled OR 4.18, (95% CI 2.20-7.98).	Kliniskt applicerbar markör?	First, second, third trimester screening Ej kliniskt applicerbar samt ingen prediktionsstudie. Exkludera.

Maria S artiklar

Yang J, 2016, USA AS	Case control observational	PE 197 White 90 Hisp 67 Black 40 C=2363	Excluded defined	w 15-20,PlGF s-Engs-VEGFR1, early-onset PE in whites, Hispanics, and blacks. Racial-ethnic differences were observed ePE (<32 0.13% for Whites 0.14% for Hispanics 0.41% for Blacks White more nulliparous (81.11% versus 50.11%, P < 0.05), Hispanic cases were older (28.61 versus 26.22 years, P < 0.05), Maternal education and gestational age not associated racial-ethnic group. Gestational age at delivery and at preeclampsia did not differ across racial-ethnic groups.		higher PlGF level lower risk for ePE in all three racial-ethnic groups, weakest associations among Blacks [AOR], 0.219CI, 0.124-0.385 [P < 0.05]; AOR, 0.048; CI, 0.026-0.088 in Whites, and AOR, 0.028; CI, 0.013-0.060 in Hispanics). Elevated sVEGFR-1 and sEng positively associated ePE. increase of sEng five-fold increase risk ePE in all three racial-ethnic groups, weakest in Blacks (AOR, 5.02, CI, 2.56-9.86 [P < 0.05] in comparison to AOR, 36.87; CI, 17.00-79.96 in Whites, and AOR, 86.68; CI, 31.46-238.81 in Hispanics). no difference PlGF and sEng early-onset preeclampsia between Whites and Hispanics. Elevated risk ePE associated with higher sVEGFR-1 in Whites (AOR, 3.24; CI, 2.04-5.14) and Hispanics (AOR, 3.68CI, 2.16-6.29) but not in Blacks (AOR, 1.2; CI, 0.7-2.1). Case control setting – over-estimation of effect? Not applicable as a prediction model, rather comparison between different racial groups.			
STEFAN									
Qiong, Lei, 2016, China						EXCLUDE Asian population			
Navaratnam, K, 2017, UK	Prospective cohort	150 women, 22 preeclampsia				EXCLUDE – to few in outcome group			

Tsiakkas, A, 2016 47:472-477, UK AS	Prospective cohort	10282 (from cohort of 40000 women with measurements in first trimester)	30000 women did not have samples taken in 2nd trimester until later in the study	Second trimester (19-24 weeks) measurement of maternal risk factors (age, race, method conception, smoking, hypertension, DM, SLE, APS, family history of PE in mother, obstetric history (parity, PE in previous pregnancy, gestational age at delivery and infant weight, interval in years after last pregnancy, estimated date of conception. Maternal weight each visit) and PlGF in combination	EOPE (<32 weeks) Sensitivity 89% with specificity 95%. Sensitivity 89% with specificity 90% EOPE (32-36+6 weeks) Sensitivity 45%, specificity 95%. Sensitivity 65%, specificity 90% LOPE (>37 weeks) Sensitivity 28% Specificity 95%, Sensitivity 37%, Specificity 90%	Serum PlGF improves detection of PE in second trimester, best for EOPE, not applicable for LOPE.			
Tsiakkas, A , 2016 47:478-483, UK AS	Prospective cohort	8079 (unclear if they originated from larger cohort)		Second trimester (19-24 weeks) measurement of maternal risk factors (age, race, method conception, smoking, hypertension, DM, SLE, APS, family history of PE in mother, obstetric history (parity, PE in previous pregnancy, gestational age at delivery and infant weight, interval in years after last pregnancy, estimated date of conception. Maternal weight each visit) and sFlt-1 in combination	EOPE (<32 weeks) Sensitivity 53% at 95% specificity, Sensitivity 73% at 90% specificity EOPE (32+1-36+6 weeks) Sensitivity 26% at 95% specificity, 48% at 90% specificity. LOPE (>37 weeks) Sensitivity 28% at 95% specificity, sensitivity 37% at 90% specificity	Addition of sFlt-1 improves detection rate for early onset PE but not LOPE but is still poor.			
Wright, A, 2016, UK AS	Prospective cohort	7597 (originated from a larger cohort in first		Second trimester (19-24 weeks) measurement of maternal risk factors (age, race, method conception, smoking, hypertension, DM, SLE, APS, family history of PE	PAPP-A no difference between groups in second and third trimester. For bhCG, it improved sensitivity for EOPE <32 weeks as a single marker	bhCG improves detection rate of EOPE slightly as a single test, not evaluated as a combination.			

		trimester of 94989 women)		in mother, obstetric history (parity, PE in previous pregnancy, gestational age at delivery and infant weight, interval in years after last pregnancy, estimated date of conception. Maternal weight each visit) and PAPP-A and b-hCG in combination vs alone	compared to maternal characteristics at 95% specificity but not at 90% specificity (sensitivity 57% vs 43% with 95% spec and 57% vs 71% at 90% spec). For EOPE 32+1-36+6, it improved detection at 95% spec (sens 43% vs 33%) but less at 90% spec (57% vs 52%). For LOPE >37 weeks, no improvement was seen. Not evaluated as a prediction model with maternal characteristics in second trimester				
Yeung, E, 2014,	Nested case control	136 controls, 71 preterm PE, 98 term PE, 101 Gestation hypertension		Levels of copeptin three times at <22 gw, 22-32 gw and at 33-38 gw for prediction of PE.	Higher levels before diagnose of preeclampsia. <22 gw aOR 1.55 (1.03-2.31) for all preeclampsia, 1.86 (1.08-3.2) for preterm PE 8<37 gw), 1.33 (0.91-2.32) for term PE.	Not clinically applicable, not included for qulity analysis			

15. Prediktion tredje trimester

PE first search
Outcome: 3rd trimester

Author, Year, Country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	Directness *	Study limitations*	Precision*	
				Intervention	Controls					
Acestor, N. 2016 Clin Chem Lab Med Nedladdad fulltext I AUC tabell	Systematic review	135 studies on biomarkers :49 blood, 9 urine		Blood and urine markers in low resource setting (2008-2013) 1st, 2nd 3rd Biomarkers divided in good, adequate and poor quality of predicting preeclampsia.	Good blood: s-Flt1, sEng, GlynFN, PlGF, sUric acid Good urine: Congophilia red, adipsin No sens/spec/AUC/OR reported.	Screening at any point in pregnancy, i. e 1st, 2nd or 3rd trimester				
Afshani N,2013,USA Nedladdad fulltext I AUC tabell	Syst review-Medline, EMBASE, Cochrane 12 articles Kaaja 1999 n=9, Borghi 2000, n=40, Folk 2005 n= 7, Kale 2005	12 observational studies (11 pro, 1 retro) 2 high quality PE pat (6-63) Rafik 2009 n=35, Tanuous 2010 n=6	Excluded well defined	proBNP and PE and heartcompl Modified cochrane review for diagnostic tests and study quality OR 30,7 Rafik n=35 (95% CI 3,8-291) OR 21 tihtonen n=19 (95% CI0.5-192) No sens/spec/AUC reported		2 studies no change in pro BNP 4 studeies hight proBNP in PE 1 study no diff norm/PE 7 of 8 studies high in PE 1 study BNP; PE>HT 5 studies high BNP-more complications	+	+	+	

	n=40, Resnik 2005 n=34, Tithon en 2007 n=19, Rafik 2009 n=35, Fustare t 2010 n=20, Moghb eli 2010 n=63, Speksni jder 2010 n=22, Tanuou s 2010 n=6	(321-22-12)								
Aghajafari, F, 2013, BMJ Nedladdad fulltext I AUC tabell	System atic and meta	31 studies		25(OH)D levels and pregnancy outcome <75nmol/L and <37,5nmol/L	Low levels associated w bacterial vaginosis, SGA, increased PE, GD Insufficient serum levels of 25-OHD Pooled OR pre-eclampsia (1.79, 1.25 to 2.58), and small for gestational age infants (1.85, 1.52 to 2.26). No DR or AUC reported.					

Akkermanns J 2014, Netherlands Nedladdad fulltext Till komplikationer	Prosp. cohort PETRA	I=216 PE C=2023	Not defined	2^{nd} 3^{rd} trim severe early PE 24-34w, External validation of fullPIERS model and adverse outcome within 48 h. For adverse outcome <48 h; AUC ROC 0.970 (95% CI 0.94 - 0.99). for adverse outcome <7 days; AUC ROC 0.800 (95% CI 0.74 - 0.85)	No validation cohort	Basic characteristics the same No validation cohort Small Retropective adding of data were laboratory values taken within 2 weeks upto 12 h after inclusion. In the study group half of the women (111) had received plasma expansion and the other half not.(105)	?	-	?	
Al-Rubaie, ZTA 2016 BJOG Nedladdad fulltext Före 17 veckor – till första trimester	System atic review	29 studies, 70 models (22 simple models)		Performance of models		Parity, PE history, race, CH, conception methods AUC 0,76 (0,67-0,90) Good table	+	+	+	

Alvarez-Fernandez, 2015, Spain Nedladdad fulltext I AUC tabell	Case-control retrospective	N=257 susp.PE <34w=62, PE 25 >34w=195,PE 49 1st, 2nd, 3rd trim	N=24	Women with 25(OH)D levels < 50 nmol/L experienced an increased risk of developing late-onset PE [odds ratio (OR) 4.6, 95% confidence interval (CI) 1.4–15], but no association was found for early-onset PE. However, a sFlt-1/PlGF ratio above the corresponding cutpoints increased the risk of developing both early- and late-onset PE [ORs 58 (95% CI 11–312) and 12 (95% CI 5.0–27), respectively]. No AUC/DR presented	<34w no PE 32 >34w no PE 146	Controls developed no PE. Results significant for 2nd and 3rd trim. Low 25OH D levels significant for >34w. 1st trim samples too few Excluded pat not defined Cut off levels for sFlt/PlGF taken from own early small study Studypop:multiple gest and IUGR more common I PE gruops	?	?	-	
Alpoim P, 2013, Brazil Nedladdad fulltext I AUC tabell	Systemic Review	2 studies in review 992 PE, 883 cntrls 2 case control studies for review		Blood groups and PE OR of 2.42 (1.63-3.58) No AUC/sens/spec presented.	AB associated w PE Increased vWF and factor VIII		?/+	?	+	
Andrietti S 2016, UK Finnsi andra sökningen I AUC tabell	Prosp cohort	C=11771 <37w790 >37w1958 GH 29483rd	Exclusion defined	3rd trim 35-37 gw n=3920 UtPI, MAP, PlGF, sFLT: risk factors Predict 84% at 10%FPR		Screening for PE in term pregnancy: w11-13 47%, 19-24 46%, 30-34 66% 35-37: 82% (70-91) the model 84% the best individual marker s-Flt	+	?	+	

Arisoy R 2016 Turkey Nedladdad fulltext I AUC tabell	Prospe ctive cohort	N=157 I=77 PE, C=180	Exclusion criteria defined but not numbers	Late 2nd and 3rd trim. Vit D: 25(OH)D Levels<20ng/mL a 12.45 OR (1.66-93.18) for severe PE No reporting od DR or AUC.		Small group of patients	+	?	?	LOW
Asvold B, 2014, Acta Obstet, Gyn Scand Nedladdad fulltext I AUC tabell	Nested -case-control	(35940) 121 preterm, 158 preterm PE, 356 controls	exclusion critera and excluded pat well defined	HCG third trimester	High human chorionic gonadotropin concentrations in the third trimester were associated with increased risk for term preeclampsia (OR 4.8, 95% CI 1.8–13.3) No AUC/DR reported		+	?	+	MEDIUM
Bredaki FE Ultrasound Obstet Gynecol, 2016 UK Nedladdad fulltext I AUC tabell	Prospe ctive Case-ctrl	17071 (488PE) cases in 11-13gw, 8583 (217PE) in 19-24, 8609 (208) in 30-34 gw	Exclusion definied	In pregnancies that developed PE, serum AFP multiples of the median (MoM) was increased at 11–13 and 19–24 weeks' gestation, but not at 30–34weeks No AUC/DR for third trimester since not significant differences.		excluded from 1st trim to 2nd and 3rd trimester is 50% lower-ie selektionbias	+	-/?	+/?	LOW

Burris HH 2014 USA Nedladdad fulltext I AUC tabell	Prosp cohort Vit D PE	2128 1591 56PE 109 GH	Exlusion defined	I=PE C=GH C2=non HT NS We did not detect an association between plasma 25(OH)D concentration (mean 58, SD 22 nmol/L) and preeclampsia. For each 25 nmol/L increase in 25(OH)D, the adjusted odds ratio for preeclampsia was 1.14 (95% confidence interval: 0.77, 1.67) o AUC/ no SENS/SPEC		Vit D level <10 gw	+	?	+	MEDIUM
Chappell LC 2013 UK Nedladdad fulltext I AUC tabell	Case control prospective multicenter	N=625 I; PE 346	Exclusion clearly shown	Predicition for PE with PlGF suspicion of PE, 2nd and 3rd trim DR at 10% FPR, prediction of PE in 14 days; assessed<35gw: 0.63 (0.51–0.74), 35-36+6w; 0.22 (0.13–0.34), >37 w 0.26 (0.17–0·36). AUC presenting <35gw with PE delivery<14 days; 0.87 (0.03)	I: low PlGF C: normal PlGF	More complicated patients I n early PE group than in later. Otherwise baseline data similar	+	+	?	
Cohen JM. 2015 Plos ONE Nedladdad fulltext Till riskfaktorgruppen Mer en case control design av manifest sjd? Exkludera? Till riskfaktorgruppen?	System atic and meta	64 studies		Antioxidant levels and PE 16% of levels measured before diagnosis of PE. The majority of included studies compared antioxidant levels in women with clinically manifest preeclampsia to third trimester controls.		Not conclusive				

De Oliveira L 2013 Brazil Nedladdad fulltext Till komplikationer	Cohort Case control	88 PE Adverse outcome 43, no adverse 45	Not defined and mentioned	Women with diagnosed preeclampsia, AUC for adverse outcome. sFlt1/PlGF 0.954 0.019 0.917–0.991 24 h Proteinuria 0.926 0.032 0.865–0.988 ALT 0.843 0.046 0.753–0.825 Platelets 0.811 0.048 0.717–0.905 Creatinine 0.719 0.054 0.613–0.825	I: high sFLt/PlGF ration C: Normal sFlt/PlGF ratio	More nulliparous in adverse outcome group Too few pat Excluded pat not mentioned	+?	-	-	LOW
Dogan E, 2014, Turkey Till riskfaktorgruppen	Case control prosp	C=80 I=80 PE ,early PE 37+late PE 43,	Not defined	s-VCAM-1 and fibronectin correlation in early and late PE 2nd 3rd trim Increased evels o fibronection and sVCAM in PE	The mean levels of sVCAM-1 and fibronectin were significantly higher in the LOP group than those in the normotensive group (p = 0.043 and 0.010 respectively). Markers were significantly different between the two hypertensive groups of pregnancy. The EOP group had a higher level of sVCAM-1 and fibronectin concentrati on than the LOP group (p = 0.01, for both markers). There was a positive correlation both between the values of plasma fibronectin and the	High risk for selection bias	-	+	?	LOW

					systolic-diastolic blood pressure measurements (r:0.43 and 0.44, respectively), and between sVCAM-1 and the systolic/diastolic blood pressure measurements (r = 0.54 and 0.64, respectively)					
Forest J, 2014, Canada Nedladdad fulltext I AUC tabell	Nested case control prosp	7929, 111 PE and 69 GH and 338 controls	Not well difined	sFLT-1 /PlGF ratio to predict early and severe PE measured in 20-32 gw Sensitivity at FPR of 10%,early onset PE 88.9 (58.2–98.8), preterm PE 50.0 (35.3–64.7) Severe PE 43.6 (31.8–56.1) All PE 36.9 (29.0–45.5) AUC early onset PE 0.977 (0.931–1.000) preterm PE 0.746 (0.638–0.853) Severe PE 0.746 (0.663–0.830) All PE 0.706 (0.645–0.768)			+	?	+	MEDIUM
Hu, G Am. J. of Clinical Sciences, 2016 Bara abstract på pubmed men case control, ingen prediction – Satt till riskfaktorgruppen	Case control	PE, 100 w severe, 75 eclampsia,215 cntrls		Nucleated red blood cells in maternal peripheral bllod Grest age 30-38w	**Correlation between number and cord blood and severity as well as Doppler**0.994 (95% CI: 0.990-0.998) with a cut-off point of 10.50, a sensitivity of 96.50% and a specificity of 96.28% (Figure 2A); the AUC of S/D in the fetal DV for the diagnosis of HDP was 0.975 (95% CI: 0.960–0.990) with a cut-off			?	+	?	LOW/ME

					point of 3.085, a sensitivity of 93.60% and a specificity of 98.14% (Figure 2B); the AUC of S/D in the umbilical artery for the diagnosis of HDP was 0.987 (95% CI: 0.981–0.994) with a cut-off point of 3.395, a sensitivity of 94.30% and a specificity of 94.88% (Figure 2C) and the AUC of S/D in the middle cerebral artery for the diagnosis of HDP was 1.000 (95% CI: 0.999–1.000) with a cut-off point of 3.21, a sensitivity of 99.30% and a specificity of 100%					
Kafkasli A, 2013J .Mat Fet and neonat Med Nedladdad fulltext Exkludera	Retrospective	N= 406 259 PE 168 mild 91 severe	Excluded due to lack of data about 40%!	Role of Doppler UtA+maternal characteristics, ASAT, ALAT, LD and platelets Doppler predictor of prematurity OR 3.3 (1.7-6.4) Severe PE predictor of bad outcome OR 4.1 (1.9-8.9)			-	?	?	
Khalil A, 2016, Ultrasound Obstet Gynecol, UK Nedladdad fulltext Till första och andra trimester	Prosp case control	C=172 GH=18 ePE= 22 lPE =22		1st, 2nd,3rd trim s-Flt, PlGF , sFLT/PlGF ratio, taken every 4th w until delivery from w 11-13. sFLT/PlGF ration 11-13w and 19-22w.	PlGF 11–13weeks 0.70 (0.54–0.87) 19–22weeks 0.77 (0.63–0.91) Longitudinal 0.79 (0.74–0.84) sFlt-1 11–13weeks 0.58 (0.44–0.73) 19–22weeks 0.73 (0.61–0.85) Longitudinal 0.74 (0.69–0.80) sFlt-1/PlGF ratio 11–13weeks 0.73 (0.60–0.86) 19–22weeks 0.79 (0.67–0.91) Longitudinal 0.85 (0.80–0.89)	PlGF lower in ePE p<0.001, PlGF lower w13in term PE and from w 27 in GH group, sFLt higher in ePE than contr (p<0.001),sFLt/PlGF ratio higher ePE and increased from w 11, Small groups	+	+	?	MEDIUM

Kurt RK, 2015, Turkey Nedladdad fulltext Case-control med redan diagnostiserade PE – riskfaktorgruppen	Case control	C=50 I=52PE	Not definied	Red cell distribution avd PE 2nd 3rd trim Red blood cell width related to Pe and severity		Prospective- likely but not clear	+	-	?	LOW
Lai J, 2013 UK Nedladdad fulltext I AUC tabell	Cohort Case control	N=4855 c=4294 PE145; GH 161 3rd trim	Excluded defined	I=50PE C=250 Assessed at 30-33 gw; Preeclampsia with delivery 34-37gw; AUC (DR at 10% FPR) for maternal history; 0.793;0.739–0.840 (35.7 (12.9–64.8)), PlGF 0.907; 0.866–0.940 (71.4 (41.9–91.4)), Free b-hCG 0.749; 0.692–0.800, (50.0 (23.1–76.9)) PlGF and free b-hCG 0.904; 0.862–0.936, (85.7 (57.2–97.8)) b-hCG/PlGF ratio 0.873; (0.827–0.911, 78.6 (49.2–95.1)) Maternal history plus PlGF 0.939; 0.903–0.965, (85.7 (57.2–97.8)) Maternal history plus Free b-hCG 0.822; 0.771–0.866, (64.3 (35.2–87.1)) Maternal history plus PlGF and free b-hCG 0.904; 0.862–0.936, (85.7 (57.2–97.8)) Maternal history plus b-hCG/PlGF ratio 0.900; 0.858–0.934, (85.7 (57.2–97.8)) Preeclampsia with delivery >37 gw; AUC for maternal		Only 50PE patients had serums samples for analysis ie one third of included at first	+?	?	-?	L

				history; 0.663 (0.604–0.717), PlGF; 0.734 (0.678–0.787), b-hCG 0.583 (0.523–0.641), PlGF and free b-hCG 0.743 (0.688–0.792), b-hCG/PlGF ratio 0.696 (0.639–0.749), maternal history plus PlGF; 0.783 (0.731–0.829), maternal history plus Free b-hCG 0.665 (0.608–0.720), maternal history PlGF and free b-hCG 0.778 (0.725–0.825), maternal history, b-hCG/PlGF ratio 0.763 (0.709–0.811)						
Lai J, 2013 UK Nedladdad fulltext I AUC tabell	Cohort case control	N=4855 c=4294 PE145; GH161 SGA without PE/GH 255 3rd trim	Excluded defined	I; PE=145, GH =161 C;4294 AUC for Maternal history intermediate PE (delivery 34-37 gw) 0.771 (0.758–0.783) late PE (delivery >37 gw) 0.756 (0.743–0.768) MAP intermediate PE 0.878 (0.868–0.887) late PE 0.810 (0.798–0.822) sBP intermediate PE 0.854 (0.843–0.864) late PE 0.786 (0.774–0.798) dBP intermediate PE 0.860 (0.849–0.870) late PE 0.792 (0.780–0.804) Maternal history with MAP intermediate PE 0.905 (0.896–0.914) late PE 0.845 (0.834–0.856) Maternal history with sBP intermediate PE 0.898			+	?	?	MEDIUM

				(0.888–0.907) late PE 0.836 (0.825–0.847) Maternal history with dBP intermediate PE 0.887 (0.877–0.896) late PE 0.841 (0.829–0.851)						
Lai J, 2014, UK Nedladdad fulltext I AUC tabell	Prosp cohort	w11-13; c=83615, PE=2140 w30-33; c=3734, PE 118 2nd	Not def	<u>30-33w:maternal charcter. PlGF, sFlt</u> DR with 10% FPR delivery all PE (63.6; 54.2- 72.2),4w (100; 82.4- 100), 6w 87.8; 75.2, 95.4) 8w (75.6; 65.4- 84) Maternal Characteristics; All PE (24.6; 17.1, 33.4), <4w (63.2; 38.4, 83.7), <6w (44.9; 30.7, 59.8), <8w (40; 29.8, 50.9) PlGF: All PE (62.7; 53.3, 71.4), <4w (100; 82.4, 100), <6w (83.7; 70.3, 92.7), <8w (74.4; 64.2, 83.1) sFlt-1 All PE (41.5; 32.5, 51), <4w (94.7; 74, 99.9), <6w (71.4; 56.7, 83.4) <8w (55.6; 44.7, 66)		Matern hist, UtPI and MAP; DR 90%, 65%, 53% for delivery within 4,6,8w	+	+?	+	MI
<u>Laskowska M, 2013, Poland</u> <u>Nedladdad fulltext</u> Redan PE diagnos (ej prediktion) . Till riskfaktorgruppen	Case control	C=65 I; 51 PE 64 PE/ IUGR 65 IUGR $2^{nd}3^{rd}$ trim	Not defiend	Homocysteine, assymetric dimethylarginin (ADMA)and IUGR and PE .Pos corr of homocsytein and ADMA between Normal and PE withourt IUGR but no corr when IUGR was presen t3rd trim Ingen AUC/DR		Maternal BMI differed- higher I PE group and Gest age older in controls than in studygroup	?	?	?	
<u>Leanos-Miranda A, 2013, Hypertension, Mexico</u> <u>Nedladdad fulltext</u>	3groups, no control group	N=501 mildPE 122	Not defined	Sflt/PlGF ration and urinary prolactin and sENG in Preeclampsia 2^{nd} and 3^{rd}	The risk for any adverse maternal outcome and for having a small-for-	Groups Differing in age, gest age, , smoking, gest age at sampling earlier in sPE and s PE and hellp	?	?	-	

Till komplikationer		severeP E 261 sPE + Hellp/ecl amspis 118		uPRL higher in SPE + HELLP sPlGF higher in mPE than sPE and SPE + help sFLT PlGF ration higher SPE and >sPE + HELLP sEng higher in sPE and >sPE + hellp	gestational-age infant was higher among women with sFlt-1/PlGF ratios, sEng, and urinary PRL level values in the highest quartile (odds ratios ≥ 2.7), compared with the lowest quartile. Both urinary PRL levels and the presence of antiangiogenic PRL fragments were more closely associated with the risk of specific adverse maternal outcomes (placental abruption, hepatic hematoma or rupture, acute renal failure, pulmonary edema, maternal death, and need for endotracheal intubation, positive inotropic drug support, and hemodialysis; odds ratios ≥ 5.7 and ≥ 4.7, respectively) than either sFlt-1/PlGF ratio or sEng alone. Ingen DR eller AUC				
Liu Y 2015 China Nedladdad fulltext För alla trimestrar I en klump – vart ska vi sätta in den?	Meta-analys	20 studies, 838 PE, 6138 controls	Excluded studies well described	Metaanalys: s-Flt1/PlGF ratio for all PE: AUC 0.88 (0.77-0.89). Sens 0.78 (95 % CI 0.67–0.86) and spec 0.84 (95 % CI 0.77–0.89) for PE detection sFlt-1/PlGF ratio for early onset PE: sensitivity of 0.94	Included studies: Kim 2007, Stepan 2007, Diab 2008, sibai 2008, Vivo 2008, Kusanovic 2009, Molvarec 2010, Ohkuchi 2010, Sunderji 2010, Verloren 2010, Chen 2012, McElrath 20112, Lehnen 2013, Odibo 2013, Villa 2013, Hanita 2014, Park 2014,	Seems to be from all three trimesters, subdivided in one table into “second trimester vs other trimesters”	+	+	?	H

Nämna i text, ej AUC tabell				(95 % CI 0.82–0.98), specificity of 0.94 (95 % CI 0.89–0.96) and AUC of 0.98	Doherty 2014, Moore 2014, Stubert 2014					
Lopez-Mendez MA 2013, Mexico Nedladdad fulltext Case control – redan diagnostiserad PE och bara jämförelse mellan grupper – riskfaktorer	Case control	N=102 I=pe 65 C=norm 37	Excluded not defined	Abnormal Doppler in PE OR 2,93 (1,2-7,3), PPV 89,2%, NPV 88,6% UtPI OR 2,6 (1.01-6,68)in pe Notch OR 9,0 (1,127-71,887) Umb OR 30,63 (1,47-639,71)	2nd 3rd	Hypertensive treatment in some of PE patients but not specified Both patients in second and third trimester- not specified which gest age	-	-	?	
Macdonald-Wallis C, 2015, UK Nedladdad fulltext I AUC tabell	Prosp. Cohort 2 cohorts	Develop. cohort 12996; 12679 +317 Validat; 3005;297 1+86PE	Excluded defined	Maternal charcter 1st and MAP w 20-36 MAP form w28 improved predicition PE **Auc** maternal char+MAP at Gw 20 0.79, gw 25 0.80, gw 28 0.81, gw 31 0.82, gw 34 0.84, gw 36 0.88 Any preeclampsia	1st2nd 3rd	Incidence in validation too few, low power?	+	+	?	M
Madazli R, 2014, Turkey Nedladdad fulltext Till komplikationer	Retrospect Case Contr	N=144 ePE 91 lPE 63 3rd	Not def	UtPI higher in ePE 71,4% vs 30,1% SGA, oligo,apgar neonat outcome higher in ePE than lPE	2nd 3rd waveform was significantly higher in the EOPE group (71.4 vs 30.1 %) (p < 0.001). The incidences of small-for-gestational age, oligohydramnios, Apgar score <7 at 5 min, stillbirth and early neonatal death rates were	Maternal characteristics not well defined	+	-	-?	

					significantly higher in women with EO-PE compared to LO-PE ($p < 0.01$). Maternal complications were only recorded in women with severe PE.					
Mc Carthy FP 2015, Ireland Hittar inte artikeln. Fråga Maria	Retrosp analysis of a prospective cohort ALSPAC	12996 validated in 3005	Not def	1^{st} 2^{nd} 3^{rd} trim Early preg characteristics in first trimester gives AUC 0.79 (0.73-0.85) and 0.88 (0.84-0.93) at 36gw+MAP. Effect of **MAP makes a different first at 28gw for PE AUC 0.84 (0.79-0.86)**	No predictive value for SGA or PTB	Short study with no major problems	+	?	?	
Payne B 2012, Cananda-world wide, (NZ,Australia, UK) Nedladdad fulltext – till komplikationer	Cohort Prospective Multicenter (8)	N=1935 of 2023	261 definied	FULL PIERS (lab crea, tpk,AST, SpO2, chest pain, gest age) for maternal complications. Within 48 hours; AUC ROC 0.76; 95% CI 0.72–0.8, and within 24 hours of admission (AUC ROC 0.81, 95% CI 0.77–0.86)	3rd	If a-missing data- before admittance.the last observation within 2 weeks before admittance and after admittance: the last data within 12 h from measurement	+	+	-	
Payne B 2014, Cananda-world wide, (Brazil, china, south africa, Canada etc) Nedladdad fulltext Till komplikationer	Cohort Prospective Multicenter	N=2081 of 2133 (C=1300 from full PIERS cohort)	52 excluded. defined	Screening for adverse outcome in hypertensive disorders;symtoms, demographics and signs: Development of miniPIERS equation: AUC for bad maternal outcome within 24 h after admission= 0.768 (95% CI 0.735–0.801	1300 from full PIERS cohort for external validation of the developed miniPIERS model 3rd.	Diffrences between pat in miniPIERS model compared to full PIERS model but correction was performed	+	?	+	
Polat I 2015, Turkey	Case-Control	N=490 PE, I=431	Defined Doppler on 442	Double notches (n=39) and bilateralnotches(n=252)	n=59 no notch 3^{rd} trim		+	?	-	

Nedladdad fulltext Till komplikationer	Retrospective	C=59 166 mild, 324 severe	Neonatal data 408	predictive of adverse maternal outcomes Ingen AUC/DR						
Rios DRA 2015, Brazil Hittar inte artikeln men verkar vara efter diagnos – till riskfaktorgruppen	Case control	N=120 I=60 PE ePE34 lPE 26 C=60	Not defined	sENG and sVCAM, and lower VEGF were found in severe PE compared to controls	C=60 No PE	The normotensive group had very varying GA with median 32w	+?	?	?	
Stubert J, 2014, Germany Nedladdad fulltext Till komplikationer	Retrosp cohort	N=68 EarlyPE=44, latePE 24	Excluded not def	Difference early o late **severe PE** and predictors 2nd and 3rd trim	Early- and late-onset severe preeclampsia differed from each other remarkably. Perinatal outcome was unfavorable in early-onset disease and seemed to be mainly a result of premature delivery and development of fetal growth restriction. Abnormal uterine Doppler velocimetry increased the risk of low 5-min Apgar values [odds ratio (OR) 8.0, P = 0.012] and preterm birth < 34+0 weeks (OR 17.9, P < 0.001). An increased resistance of the umbilical artery was associated with a higher risk for SGA birth weight (OR 4.9, P = 0.010) Ingen AUC eller DR	UtPI abnormal; increase risk low apgar OR 8.0 and preterm OR 17,9 SGA OR 4,9	-	?	?	

Tayyar A 2014 UK Nedladdad fulltext I AUC tabell	Prosp screening	N=83615 normotensive 2140 PE but this study I=360 PE C=13878 normotensive	Not defined which were excluded from the primary cohort	MoM UtPI and maternal character at 30-33 gw could iidentify 90% of pregnencies developing PE-false pos rate of 5%	DR of Maternal characteristics, MAP and uterine artery PI for all preeclampsia at 10% FPR; 60.9 (55.5 – 66.0), for PE<4 weeks; 93.1 (83.3 – 98.1), for PE<6w 74.4 (66.2 – 81.6), for PE<8w 65.9 (59.9 – 71.6) DR for uterine artery at 10% FPR, all PE 48.6 (43.2 – 53.9), PE<4w 89.7 (78.8 – 96.1), PE <6w 66.9 (58.2 – 74.8), PE<8w 54.4 (48.3 – 60.5) DR for MAP at 10% FPR, all PE 1 (53.8 – 64.3), PE<4w 81.0 (68.6 – 90.1), PE<6w 68.4 (59.8 – 76.2), PE<8w 60.0 (53.9 – 65.9)	A first trim screening was also done+maternal characteristics Complete set for 350 PE and 13 878 cntrls PI higher in Afro-Carribean	+	-?	+?
Tayyar A 2016 UK Nedladdad fulltextÏ AUC tabell	Prosp cohort	w 11-13=7734 w19-24=31120 w 30-34 29802 w 35-37 5543	Not defined	MAP and maternal history DR at 10% FPR Assessed at 30-34 gw for preterm preeclampsia (delivery <37 gw); Maternal factors 44 (36–53), Maternal factors and MAP; 79 (72–86). For term preeclampsia; Maternal factors 40 (36–45), maternal factors and MAP; 53 (49–57) Assessed at 35-37 gw for term preeclampsia; Maternal factors: 33 (23–44), maternal factors and MAP; 62 (51–72)			+	?	?
Wright A, 2016; UK Nedladdad fulltext	Cohort	W 11-13=9498 9	Not well defined	Assessed at 30-33 gw, DR with 10% FPR for PE delivery <37 gw;		Combination of maternal factors with PAPP A and beta HCG improved prediction	+/?	?	?

I AUC tabell	Case contr ol	W 19-24 7597 30-34w=808 8		Maternal risk factors; 42 (26–59), PAPP-A; 55 (38–71), bhCG; 63 (46–78), combined; 63 (46–78). PE delivery> 37 gw; Maternal risk factors; 34 (26–42), PAPP-A; 36 (29–44), bhCG; 39 (31–47), combined; 37 (30–46)					
Wright D, 2016, Ultrasound Obstetr gynecol, UK Nedladdad fulltext Till andra trimester	Prosp cohort case control	N=11771 0 no PE Early PE 790 Late PE 1958 GH 2948	Exclusion not clear	Two stage screening with MAP, and history 1st trim and ultralsound and PIGF in 2nd trim With 10% false positive UtPI w 11-14; Pre early onset: sens 47,8%(39,0-56,8), spec 92,1% (88,6-94,6), pred early IUGR: sens 39,2%, (26,3-53,8), spec 93,1%, (90,6-95,0), ane PE or IUGR; sens 26,4% (22,5-30,8), spec 93,3% (90,0-95,1))	Detectionrate MAP, UtPI, Plgf; 74%, 2 stage screen MAP maternal first and utPI plgf second; detec rate 71% with 50% less examinated. Screen at 19-24w: det rate MAP, maternal UtPI plgf; 84%, 2 stage det rate only 70%. If 30% was offered screen and and higher if 405 was offered	Very low numbers of patients undergping measurement with Plgf and varying sizes o grupps amalyzed	+/?	?	?
Wright D, 2016, Ultrasound Obstetr gynecol, UK Nedladdad fulltext I AUC tabell	Prosp cohort case control	19-24w C=7318 PE=247 30-34W C=8021 PE=243	Excluded not defined	AUC (DR at 10% FPR) at 30-32 gw for PE delivery <4w; Maternal factors; 0.7855; 0.7497–0.8212, (46 (38–54)) Maternal factors and sFlt-1; 0.9594; 0.9292–0.9895, 88 (72–97) <6w: Maternal factors 0.7735; 0.7484–0.7985, (46 (40–51)) Maternal factors and sFlt-1; 0.9237; 0.8950–0.9525, 84 (76–91) <37 w; Maternal factors; 0.7844; 0.7513–0.8174, (45 (37–52)) Maternal factors and sFlt-1; 0.9658; 0.9440–0.9876, (94 (82–99)) >37w; Maternal factors;		in a large cohort sFlt was measure in some pat that are included, total population 123406	+/?	?	?

				0.7495; 0.7285–0.7705, (41 (37–45)) Maternal factors and sFlt-1; 0.8052; 0.7723–0.8382, (51 (44–58))						
Zeisler H, 2016, Multicenter Nedladdad fulltext I AUC tabell	Prospective multicenter	500 development cohort 550 validation 101+98 PE		AUC for Flt/PlGF PE <1w; development cohort 89.8% (95% CI, 83.6–96.0), validation cohort 86.1% (95% CI, 79.8–92.4). AUC for PE <4w: development cohort; 86.1% (95% CI, 80.9–91.3) validation cohort; 82.3% (95% CI, 77.3–87.3)	Cutoff value of 38 <38 negative predictive value within a week 99.3% 80%sens, 78,3% spec >38 positive predictive value within 4 weeks 36,7% at 66% sens and 83,1 spec		+	+	+/?	
Agrawal, S., et al. (2018). Hypertension **71**(2): 306-316 Several countries, all continents AS Finns i AUC tabell	Systematic review and meta analysis for sFlt/PlGF ratio in predicting onset of preeclampsia	15 studies, 18 groups when divided on outcome early/late PE. 534 PE, 19587 controls	No dropouts after specified inclusion criteria (originally 3736 studies)	Overall: sens 80% =.68-0.88), spec 92% (0.87-0.96). High risk group: sens 85% (0.66-0.94), spec 87% (0.76-0.93), low risk group sens 77% (0.61-0.88), spec 94% (0.88-0.97). Post-test probability Neg LR 7%	Kliniskt applicerbar		19-37 gw, prediction of preecl both early and late Heterogeneity in studies. Andra och tredje trimester, pre av senare preeklampsidiagnos			
Andersen, L. B., et al. (2016). Hypertens Pregnancy 35(3): 405-419 Denmark I AUC tabell	Prospective cohort	6707 were offered inclusion and 2874 (42.9%) enrolled A total of 1909 blood samples were available		Concentrations of sFlt-1, PlGF, and sFlt-1/PlGF in GW20-34 were predictive of PE development, but not in GW8-14. PlGF outperformed sFlt-1/PlGF ratio with an area under curve (AUC) of 0.755 vs. 0.704, p = 0.002. The highest AUC values for PlGF and sFlt-1/PlGF ratio were seen for severe early-onset PE (0.901	Kliniskt applicerbar. PlGF och Flt-1		First and second, third tr screening for preeclampsia Relativ låg AUC för att fungera single screeningtest. Bör även läggas till i 3:e trim			

				and 0.883). Negative predictive values were high for all PE types, but positive predictive values were low.		
Andrietti, S., et al. (2017). Ultrasound Obstet Gynecol 50(2): 221-227 United Kingdom Finns i AUC tabell	Prospective cohort	Complete data for biomarkers: 3663 healthy, 136 PE. Overall 123406 pregnancies		AUC:s for maternal risk factors, PlGF, UtAPI presented for first, second, third trimester for PE <37 weeks and >37 weeks. Also combinations of measurements in all 3 trimesters. Conclusion that a combination did not lead to higher AUC. See article for all numbers.	Kliniskt applicerbara markörer	Large cohort but for bio smaller. First, second and third tr screening
Andrietti, S., et al. (2016). Ultrasound Obstet Gynecol 48(1): 72-79 United Kingdom Finns i AUC tabell	Prospective cohort	123406 total with maternal data,	unclear how much data missing for PlGF and UTPI		Kliniskt applicerbara markörer	Third trimester screenin detection of preeclampsia for each case of PE (n=2748) and pregnancie unaffected by PE or PIH (n=117 710), the biophysical a biochemical MoM values were simulated from the fitte multivariate Gaussian distribution for log-transformedMoMvalues
Duckworth, S., et al. (2016). PLoS ONE 11(10): e0164276 United Kingdom and Ireland Exkluderas	Prospective cohort	132		Cost effective analysis of the use of PlGF as aid in diagnose.	Kliniskt applicerbar markör Ska vi ta med denna eller ej? Kostnadsanalys.	PlGF in women with elevate third trimester. Algorithm i admissions where we normal admit in Sweden. Not generali
Ferguson, K. K., et al. (2017). Am J Obstet	Prospective cohort	50 mothers who experienced		At visit at 18 weeks; hazard ratios for a combination of 8-isoprostanel 8-	Inflammations och oxidative stressmarkörer för PE	urine and plasma samples at points during gestation (med 18, 26, and 35 weeks). Predi first, second and third trimeste

Gynecol 216(5): 527.e521-527.e529 USA Finns i AUC tabell		preeclampsia and 391 mothers with normotensive pregnancies		hydroxydeoxyguanosine, C-reactive protein, the cytokines interleukin-1b, -6, and -10, and tumor necrosis factor-a showed an increased risk of preeclampsia with 1.31-1.83, in association with an interquartile range increase in biomarker. Hazard ratios at this time point were the most elevated for Creactive protein, for interleukin-1b, -6, and -10, and for the oxidative stress biomarker 8-isoprostane (hazard ratio, 1.68; 95% confidence interval 1.14-2.48)	Inga AUC eller sens/spec beskrivna i artikeln.	
Frusca, T., et al. (2017). J Matern Fetal Neonatal Med 30(18): 2166-2173. Italy exkludera	Cost effective analysis	Derived from PROGNOSIS study and calculated on an expected rate of 49500 women with suspected PE/year		sFlt-1/PlGF ration in predicting preeclampsia at 28-32 gw. Healthcare costs associated with the management of a pregnant woman with clinical suspicion of PE equal 2384 euros when following standard practice versus 1714 euros using sFlt-1/PlGF ratio test.	Kliniskt applicerbara markörer Kosteffektiv analys – inte i AUC tabellen – beskrivs i text?	Screening for preeclampsia i trimester (28-32 weeks) fo diagnosis of preeclampsia
Anna						

Koning, S. H., et al. (2016). Netherlands. Finns även i 1 och 2 trimester	Retrospective cohort	820		GDM patients. Comparison regular treatment diet-only vs additional insulin therapy. No differences between	No adjusted analyses. Ingen prediktion.	First, second, third trimester screening.

Exkluderas AS				the group regarding PE.		
Leavey, K., et al. (2016). Canada. Finns även i 1 och 2 trimester Exkluderas AS??/ej mall		330 human placenta microaaray dataset including 7 previously published studies and 157 highly annotated new samples from a Biobank.		Aim: To find clinically differences between subclasses of PE and insight into potential contributors of individual maternal factors in the development of specific types of PE.		???? First, second and third trimester screening
Laskowska, M. (2017). Poland. Finns även i 2 trimester Ej inkludera? AS/ej mall	Case-control.	125/20eoPE/31loPE/ 65 healthy		Levels of maternal serum matrix metalloproteinases NMP-2, -3, -9, -13. Higher MMP-3 early onset PE, not late onset. Higher MNP-2, -13 and lower levels of MMP-9 related to both eoPE and loPE.	Ej kliniskt applicerbar markör	Second and third trimester screening
Lagana, A. S., et al. (2018). Italy. Finns även i 1 och 2 trimester Exkludera? AS	Review Case-control studies	12 studies		Role of miRNA in PE onset both as increased or decreased expression in placenta or as maternal serum markers.	Se results. Ej kliniskt applicerbar markör	First, second, third trimester screening
Kwiatkowski, S., et al. (2016). Poland. Finns även i 2 trimester AS	Case-control.	83 PE/of whom 42 eoPE, 41 loPE(>34 gw). 43 controls		eoPE andloPE and control (and IUGR). Statistically significant for PE groups D-dimer higher and APTT lower than in control group. S-Flt higher, PlGF lower, S-Flt-1/PlGF	Kliniskt applicerbar markör Exkludera – ingen prediction?	Second and third trimester screening

				ratio higher, Il-6 and hsCRP higher I PE groups than controls.		
Kwiatkowski, S., et al. (2017). Poland. Nivåer av biomarkörer efter diagnos – ingen prediction. Exkludera	Case-control.	83 PE/of whom 42 eoPE, 41 loPE(>34 gw). 76 controls		S-Flt-1 and PlGF and S-Flt-1/PlGF ratio. Concentrations in different stages of pregnancy. Lower PlGF concentrations in eoPE than in loPE. Opposite in control group. In PE groups no differences in SFlt-1 concentrations. Increased concentration in the group of physiological pregnancies after 34 gw. SFlt-1/PlGF ratio values higher in eoPE than in loPE and in control group.	Kliniskt applicerbar markör	Second and third trimester screening
Kurtoglu, E., et al. (2016).Turkey. Finns även i 2 trimester Hittar ej artikeln	Case-control.	250/100 NT/121 sPE/29 mPE		Platelet count, mean platelet volume, platelet distribution,width, platelet crit. Samples at time of admission. Samles from normal pregnancies were taken at last antenatal visit prior to delivery. Mean platelet volume and platelet distribution width was significantly higher in	Kliniskt applicerbar markör?	Second and third trimester screening?

				PE group (p=0.006 and 0.046) Platelet count, mean platelet volume, platelet crit was increased in late onset PE (p<0.05)		
Leme Galvao, L. P., et al. (2016). Brazil. Finns även i 1 och 2 trimester Exkludera	Case-control.	Case-control 456 (169 severe preeclampsia,287 controls)		High pregestational BMI aOR 2.77 (1.75-4.38), p<0.001, first gestation 1.85 (1.18-2.92) p<0.008, low level of consciousness on admission 3.31 (1.30-8.42) p=0.01,2 associated with severe PE in multivariable analyses. IL1B genotype were associated only in univariate analyses.	Kliniskt applicerbar markör	First, second, third trimester screening
Lei, J., et al. (2016).International/China. Finns även i 1 och 2 trimester Ej inkludera/För diskussion? AS	Meta-analys and own studies.	6 included studies of pregnant women. 301 PE/456 non gravida hypertension/344 controls.		Angiotensin II tpe 1 receptor autoantibody (AT1-AA) was associated with PE poopled OR 32.84, (95% CI 17.19-62.74) but weaker with non-pregnant hypertension pooled OR 4.18, (95% CI 2.20-7.98).	Kliniskt applicerbar markör?	First, second, third trimester screening
MARIAS, 3:e trim, 2a sökningen						

Seshadri Reddy V,	Systematic	Six case control studies		Ischemia-modified albumin IMA		All from india and turkey			

2018, tureky and india EXKLUDERA	review and meta analysis	PE 57+8+20+22+36 +19 C: 57+80+19+22+1 8+19		IMA in detecting PE sensitivity; 0.80 (CI 0.73-0.86), specificity; 0.76 (95%CI 0.70-0.81), DOR; 14.32 (95%CI 5.06-40.57), and AUC; 0.860.					
Sovio U, 2017, UK **Finns I AUC tabell**	Prosp case-control	N=4099, w20= 3989, w28=3776, w36= 3776	Exclusion well defined	POP study, at ≈20, ≈28, and ≈36 weeks of gestational age (wkGA., Sflt/PlGF ratio 28 wsFlt-1:PlGF ratio >38 (PPV) of 32% PE and preterm birth, PPV similar low and high prior risk. 36 w sFlt-1:PlGF ratio >38 PPV sPE 20% high-risk ,6.4% in low-risk 36 wsFlt-1:PlGF ratio >110 PPV 30% sPE, 36 w 195 (5.2%) either sFlt-1:PlGF ratio >110 or sFlt-1:PlGF ratio >38 plus maternal risk factors: 43% developedPE, low-risk 36 w sFlt-1:PlGF ratio ≤ 38 NPV sPE 99.2%.					
Tan MY, 2017, UK. Finns I AUC tabell	Case control pros Cohort	N=8063 PE=231	Not well defined, see former study	observational study ultrasound scan at 31-34 weeks ,maternal (MoM) (PlGF) (sFlt-1) compare sFlt-1/PlGF ratio. Bayes' theorem similar to sFlt-1/PlGF ratio (AUC, 0.987 (95% CI,		Har flyttats från andra trimestern. AS			

				0.979-0.995) vs 0.988 (95% CI, 0.981-0.994); P = 0.961) delivery with PE at ≥ 4 weeks after to 40 w better Bayes' theorem than sFlt-1/PlGF ratio (AUC, 0.884 (95% CI, 0.854-0.914) vs 0.818 (95% CI, 0.775-0.860); P < 0.0001)					
Tsiakkas A, 2016, UK Finns I AUC tabell	Cohort	N=40122 1st trim w 11-13 N2=10282 19-24w N3=10400 30-34w N4= 4043 35-37w	Exclusion not so well defiend	PlGF 11-13 w 19-24 w at 30-34 w 35-37 weeks. Bayes' theorem was used DRs at FPR 10%, for PE deliv< 32 w 79% and 97% with screening at 12 and 22 wThe DRs for PE deliv 32 + 0 to 36 + 6 w were 57%, 65% and 90% with screening at 12, 22 and 32 weeks. The DRs for PE delivering ≥ 37 weeks were 40%, 37%, 54% and 64% with screening at 12, 22, 32 and 36 weeks, respectively.		Controll gruppen större i denna studie än i den nedan med Sflt trots att det verkar vara samma cohort!			
Tsiakkas A, 2016, UK Finns I AUC tabell	Cohort	N1=7066 11-13w, N2≈8079 19-24w, N3= 8472 30-34w, N4=4043	Exclusion not so well defiend	sFlt-1w 11-13,w19-24 w30-34 w 35-37. Bayes' theorem , sFlt-1. PE delivery < 32, between 32 + 0 and 36 + 6 and ≥ 37 w. sFlt-1 11-13 w did not improve prediction, sFlt-1 at 19-24 w improved pred < 37 w		Control group samller than in plgf study though it seems to be the same cohort.			

				but not delivering ≥ 37 w. sFlt-1 at 30-34 w improved pred PE delivering < 37 and PE delivering ≥ 37 w. sFlt-1 at 35-37 w improved pred PE deliv ≥ 37 w. DRs FPRof 10%, PE deliv < 32 w52% and 65% with screening at 12 and 22 w, respectively. DRs for PE deliv 32 + 0 and 36 + 6 w 44%, 44% and 93% with screening at 12, 22 and 32 weeks. DR for PE deliv ≥ 37 weeks were 37%, 37%, 52% and 69% with screening at 12, 22, 32 and 36 weeks, respectively.					
Visentin S, 2017, Italy Ej AUC tabell – ej kliniskt applicerbar, inkluderar bara gestational hypertensio	Observational prosp case/control	N=1381 C=1308 GH=73	Excluded well defined	UtAs Doppler w 29-32,fetal biometry, fetal wellbeing, Maternatl Doppler, Fetal abd aorta intima-media thickness, fetal kidney volume AUC 81.07% (CI 75.83%–86.32%) Late-gestational hypertension predicted fetal aIMT 29 to 32 w' Doppler waveforms,		Tredje trimester. Flyttad från andra trimestern.			

n - exkludera				and maternal clinical parameters					
Wright A, 2016, UK i AUC tabell	cohort	C1 =92800 PE1 2189 C2=7396 PE2 =201 C3=7895 PE3=193	Not defined	(PAPP-A) (β-hCG) at 12, 22 and 32 w' developing (PE) preterm PE < 37 w, PE ≥ 37 w 10%FPR, preterm PE maternal factors 45% to 51% and 53% by combined screening with PAPP-A at 11-13 weeks and 30-34 w, 55% and 54% by combined screening free β-hCG at 19-24 weeks and 30-34 weeks, respectively.					
Yeung EH, 2014, USA Ej med i AUC tabell, med i sammanfattande text?	Case control secondary analysis	c 136 PE=169 GDM =92 GH=101 PTB=86	Defined but many	Copeptin 1st, 2nd and 3rd trim. Copeptin increasing with gest age cases and controls but higher with preeclampsia. Baseline copeptin 16 w aOR CI 1.55 per log unit; 1.03–2.31) (*P*=0.03)	Icke kliniskt applicerbar?				
Stefan									

Wright, A, 2016, UK AS Även i andra trimester I AUC tabellen.	Prospec tive cohort	7597 (originated from a larger cohort in first trimester of 94989 women)		Second and thirdtrimester (19-24 weeks and 30-34 week) measurement of maternal risk factors (age, race, method conception, smoking, hypertension, DM, SLE, APS, family history of PE in mother, obstetric history (parity, PE in previous pregnancy, gestational age at delivery and infant weight, interval in years after last pregnancy, estimated date of conception. Maternal weight each visit) and PAPP-A and b-hCG in combination vs alone	PAPP-A no difference between groups in second and third trimester. For bhCG, it improved sensitivity for EOPE <32 weeks as a single marker compared to maternal characteristics at 95% specificity but not at 90% specificity (sensitivity 57% vs 43% with 95% spec and 57% vs 71% at 90% spec). For EOPE 32+1-36+6, it improved detection at 95% spec (sens 43% vs 33%) but less at 90% spec (57% vs 52%). For LOPE >37 weeks, no improvement was seen. Not evaluated as a prediction model with maternal characteristics in second trimester	bhCG improves detection rate of EOPE slightly as a single test, not evaluated as a combination.			
Wright D, 2017, UK	cohort	N=8128 PE =234	Not defined	patient-specific risk of pre-eclampsia (PE) at 30-34 maternal (MAP), (UtA-PI), (PlGF) (sFlt-1)		Flyttad från andra trimestern.			

Ingen AUC/DR men med I AUC tabell				high-risk 90% PE at < 4 weeks and 40% with PE at 4 weeks from assessment to 40w. intermediate-risk 49 PE at 4 weeks from assessment to 40 w. low-risk group, none developed PE at < 4 weeks and 0.3% PE at 4 weeks to 40w					

16 Prediktion komplikationer

Prediktionsmodeller av komplikationer

Prediktor	**Lehnen H 2013 kohort** medel	**Akkermanns 2014 kohort** medel	**Leanos-Miranda 2013 kohort** medel	**Bahlmannn 2016, kohort** medel	**De Oliviera, 2013 kohort** låg	**Dragan 2017 kohort** medel	**Dragan 2017 kohort (delad)** medel	**Duckworth 2017 kohort** medel	**Payne 2012 kohort** medel	**Payne 2014 kohort** medel	**Polat 2015 retrospektiv kohort** låg	**Saleh 2016 kohort** medel	**Zeisler 2016, kohort** medel	**Almeida 2017 retrospektiv kohort** medel	**Leanos-Miranda 2017 fall kontroll** låg	AUC Preeklampsi som kräver förlossning < 1-4 weeks	AUC organkomplikationer	Detektionsgrad (x% falskt positiva) för förlossning på grund av preeklampsi	Detektionsgrad (x falskt positiva) för komplikationer på grund av preeklampsi	GRADE
Kommentar	Kan inte få fram		Maternal and perinatal morbidity OR		Adverse maternal outcomes				FULL PIERS Maternal complications	MiniPIERS Bad maternal outcome within 24 h after admission	Maternal and neonatal adverse outcomes EJ AUC/DR									
sFlt-1/PlGF ratio				x¨ 78.5% (20%) delivery due to PE	x AUC 0.954	x¨ 78.6% (4.5%) < 1w, 76.6% (4.1%) < 4w	x¨ 75.9 (FPR 1.7% gw31-34 vs 9.6%					x¨ 86% (7%)	x		x			78.6% (4.5%) < 1w, 75.9-76.6% (1.7-9.6%) < 4w,	86% (7%)	++/+++

				at any point			gw 35-47)										20.7% (4.3%) >4w 78.5% (20%) any point		
PlGF			x	x¨ 74.6 % (28.6 %) delivery due to PE at any point				x* 0.87, (0.83–0.92)							x	0.87 <2w		74.6 % (28.6 %) any point		++
sFlt-1			x	x¨ 83.7 % (31.9%) delivery due to PE at any point				x* 0.83, (0.78–0.88)							x	0.83 <2w		83.7% (31.1%) any point		++
sEng			x					x* 0.83, (0.79–0.88)							x	0.83 <2w				+/++
ALT					X AUC 0.843												0.843			+
24 h Proteinuria					X AUC 0.926												0.926			+
Platelets					X AUC 0.811												0.811			+
Creatinin					X AUC 0.71												0.719			+

					9															
Urinary prolactin			X																	+
Notch a. uterina											x									+
PIERS; Graviditetslängd, bröstsmärta, TPK, ASAT, kreatinin, POX		X AUC 0.970 (95% CI 0.94 - 0.99). for adverse outcome <7 days; AUC 0.800 (95% CI 0.74 - 0.85)							X AUC Within 48h AUC 0.76 and within 24 hours of admission AUC 0.81						x* 0.72 (0.67 – 0.77		Within 48h AUC 0.76 and within 24 hours of admission AUC 0.8	0.72			++/+++
Mini PIERS (symptom, demografiska variabler, vitalparametrar) <24 h										x AUC 0.768							0.768				+

*AUC redovisad

¨ Detektionsgrad redovisad