Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Stroke & Pregnancy Consensus Statement

Secondary Stroke Prevention and Pregnancy

Part Two: Vascular Risk Reduction

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Canadian Stroke Best Practice Recommendations

STROKE IN PREGNANCY Writing Group

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Published Guidelines

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5.1.1 Use of Anticoagulants/Antiplatelet during Pregnancy	
Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA: **Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American heart association/American stroke association.** **Stroke 2014;45:2160-2236.**	In the presence of a high-risk condition that would require anticoagulation outside of pregnancy, the following options are reasonable: a. LMWH twice daily throughout pregnancy, with dose adjusted to achieve the LMWH manufacturer's recommended peak anti-Xa level 4 hours after injection, or b. Adjusted-dose UFH throughout pregnancy, administered subcutaneously every 12 hours in doses adjusted to keep the midinterval aPTT at least twice control or to maintain an anti-Xa heparin level of 0.35 to 0.70 U/mL, or c. UFH or LMWH (as above) until the 13th week, followed by substitution of a VKA until close to delivery, when UFH or LMWH is resumed (Class IIa; Level of Evidence C). For pregnant women receiving adjusted-dose LMWH therapy for a high-risk condition that would require anticoagulation outside of pregnancy, and when delivery is planned, it is reasonable to discontinue LMWH ≥24 hours before induction of labor or caesarean section (Class IIa; Level of Evidence C). In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, UFH or LMWH, or no treatment may be considered during the first trimester of pregnancy depending on the clinical situation (Class IIb; Level of Evidence C). In the presence of a high-risk condition that would require anticoagulation outside of pregnancy, it is reasonable to use warfarin, UFH, or LMWH (Class IIa; Level of Evidence C). In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, low-dose aspirin use may be considered (Class IIb; Level of Evidence C).
Chan WS, Rey E, Kent NE, Chan WS, Kent NE, Rey E, et al. **Venous thromboembolism and antithrombotic therapy in pregnancy.** **J Obstet Gynaecol Can 2014 Jun;36(6):527-53. (selected)**	Therapeutic dose anticoagulation should be initiated for confirmed cerebral venous thrombosis. (II-2A) Thromboprophylaxis should be considered in future pregnancies following a cerebral venous thrombosis. (II-1C)
Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th	3.0.4. For pregnant women, we recommend avoiding the use of oral direct thrombin (eg, dabigatran) and anti-Xa (eg, rivaroxaban, apixaban) inhibitors (Grade 1C). 4.0.1. For lactating women using warfarin, acenocoumarol, or UFH who wish to breastfeed, we recommend continuing the use of warfarin, acenocoumarol, or UFH (Grade 1A). 4.0.4. For breast-feeding women, we recommend alternative anticoagulants rather than oral direct thrombin (eg, dabigatran) and

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ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl):e691S-e736S. **(selected)**	factor Xa inhibitors (eg, rivaroxaban, apixaban) (Grade 1C) 4.0.5. For lactating women using low-dose aspirin for vascular indications who wish to breastfeed, we suggest continuing this medication (Grade 2C) 7.1.4. For pregnant women receiving adjusted dose LMWH therapy and where delivery is planned, we recommend discontinuation of LMWH at least 24 h prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (Grade 1B). 8.2.4. For pregnant women receiving long-term vitamin K antagonists, we suggest adjusted-dose LMWH or 75% of a therapeutic dose of LMWH throughout pregnancy followed by resumption of long-term anticoagulants postpartum, rather than prophylactic-dose LMWH (Grade 2C). 10.2.1. For women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation), we recommend screening for APLAs (Grade 1B). 10.2.2. For women with a history of pregnancy complications, we suggest not to screen for inherited thrombophilia (Grade 2C). 10.2.3. For women who fulfill the laboratory criteria for APLA syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic- or intermediate dose UFH or prophylactic LMWH combined with low-dose aspirin, 75 to 100 mg/d, over no treatment (Grade 1B). 10.2.4. For women with inherited thrombophilia and a history of pregnancy complications, we suggest not to use antithrombotic prophylaxis (Grade 2C). 11.1.1. For women considered at risk for preeclampsia, we recommend low-dose aspirin throughout pregnancy, starting from the second trimester, over no treatment (Grade 1B). 11.2.1. For women with two or more miscarriages but without APLA or thrombophilia, we recommend against antithrombotic prophylaxis (Grade 1B). 12.1.1. For pregnant women with mechanical heart valves, we recommend one of the following anticoagulant regimens in preference to no anticoagulation (all Grade 1A): (a) Adjusted-dose bid LMWH throughout pregnancy. We suggest that doses be adjusted to achieve the manufacturer's peak anti-Xa LMWH 4 h postsubcutaneous-injection or (b) Adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 h in doses adjusted to keep the mid-interval aPTT at least twice control or attain an anti-Xa heparin level of 0.35 to 0.70 units/mL or (c) UFH or LMWH (as above) until the 13th week, with substitution by vitamin K antagonists until close to delivery when UFH or LMWH is resumed. *Remarks: For pregnant women with mechanical heart valves, the decision regarding the choice of anticoagulant regimen is so value and preference dependent (risk of thrombosis vs risk of fetal abnormalities) that we consider the decision to be completely individualized. Women of childbearing age and pregnant women with mechanical valves, should be counseled about potential maternal and fetal risks associated with various anticoagulant regimens, including continuation of vitamin K antagonists with substitution by LMWH or UFH close to term, substitution of vitamin K antagonists by LMWH or UFH until the 13th week and then*

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	close to term, and use of LMWH or UFH throughout pregnancy. Usual long-term anticoagulants should be resumed postpartum when adequate hemostasis is assured. 12.1.2. In women judged to be at very high risk of thromboembolism in whom concerns exist about the efficacy and safety of UFH or LMWH as dosed above (eg, older generation prosthesis in the mitral position or history of thromboembolism), we suggest vitamin K antagonists throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery rather than one of the regimens above (Grade 2C). *Remarks: Women who place a higher value on avoiding fetal risk than on avoiding maternal complications (eg, catastrophic valve thrombosis) are likely to choose LMWH or UFH over vitamin K antagonists.* 12.1.3. For pregnant women with prosthetic valves at high risk of thromboembolism, we suggest the addition of low-dose aspirin, 75 to 100 mg/d (Grade 2C).
Gordon H. Guyatt , MD, FCCP ; Elie A. Akl , MD, PhD, MPH ; Mark Crowther , MD ;David D. Gutterman, MD, FCCP; Holger J. Schünemann, MD, PhD, FCCP; for the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel **Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians: Evidence-Based Clinical Practice Guidelines, Executive Summary** **CHEST 2012; 141(2)(Suppl):7S–47S (selected)**	4.0.4. For breast-feeding women, we recommend alternative anticoagulants rather than oral direct thrombin (eg, dabigatran) and factor Xa inhibitors (eg, rivaroxaban, apixaban) (Grade 1C). 4.0.5. For lactating women using low-dose aspirin for vascular indications who wish to breastfeed, we suggest continuing this medication (Grade 2C). 11.1.1. For women considered at risk for preeclampsia, we recommend low-dose aspirin throughout pregnancy, starting from the second trimester, over no treatment (Grade 1B). 11.2.1. For women with two or more miscarriages but without APLA or thrombophilia, we recommend against antithrombotic prophylaxis (Grade 1B).
Saposnik G, Barinagarrementeria F, Brown R, et al. **Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American**	1. For women with CVT during pregnancy, LMWH in full anticoagulant doses should be continued throughout pregnancy, and LMWH or vitamin K antagonist with a target INR of 2.0 to 3.0 should be continued for at least 6 weeks postpartum (for a total minimum duration of therapy of 6 months) (Class I; Level of Evidence C). 2. It is reasonable to advise women with a history of CVT that future pregnancy is not contraindicated. Further investigations regarding the underlying cause and a formal consultation with a hematologist and/or maternal fetal medicine specialist are reasonable. (Class IIa; Level of Evidence B). 3. It is reasonable to treat acute CVT during pregnancy with full-dose LMWH rather than UFH (Class IIa; Level of Evidence C). 4.

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Heart Association/ American Stroke Association. ***Stroke* 2011; 42(4):1158–1192.**	For women with a history of CVT, prophylaxis with LMWH during future pregnancies and the postpartum period is probably recommended (Class IIa; Level of Evidence C).
5.1.2 Hypertension during Pregnancy	
Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, Howard VJ, Lichtman JH, Lisabeth LD, Piña IL, Reeves MJ, Rexrode KM, Saposnik G, Singh V, Towfighi A, Vaccarino V, Walters MR; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Council for High Blood Pressure Research. **Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:•••–•••.**	**Prevention of Preeclampsia** 1. Women with chronic primary or secondary hypertension or previous pregnancy-related hypertension should take low-dose aspirin from the 12th week of gestation until delivery (Class I; Level of Evidence A). 2. Calcium supplementation (of ≥1 g/d, orally) should be considered for women with low dietary intake of calcium (<600 mg/d) to prevent preeclampsia (Class I; Level of Evidence A). **Treatment of Hypertension in Pregnancy and Postpartum** 1. Severe hypertension in pregnancy should be treated with safe and effective antihypertensive medications, such as , with consideration of maternal and fetal side effects (Class I; Level of Evidence A). 2. Consideration may be given to treatment of moderate hypertension in pregnancy with safe and effective antihypertensive medications, given the evidence for possibly increased stroke risk at currently defined systolic and diastolic BP cutoffs, as well as evidence for decreased risk for the development of severe hypertension with treatment (although maternal-fetal risk-benefit ratios have not been established) (Class IIa; Level of Evidence B). 3. Atenolol, angiotensin receptor blockers, and direct renin inhibitors are contraindicated in pregnancy and should not be used (Class III; Level of Evidence C). 4. After giving birth, women with chronic hypertension should be continued on their antihypertensive regimen, with dosage adjustments to reflect the decrease in volume of distribution and glomerular filtration rate that occurs after delivery. They should also be monitored carefully for the development of postpartum preeclampsia (Class IIa; Level of Evidence C). ***Prevention of Stroke in Women with a History of Preeclampsia*** 1. Because of the increased risk of future hypertension and stroke 1 to 30 years after delivery in women with a history of preeclampsia *(Level of Evidence B)*, it is reasonable to (1) consider evaluating all women starting 6 months to 1 year post partum, as well as those who are past childbearing age, for a history of preeclampsia/eclampsia and document their history of preeclampsia/eclampsia as a risk factor, and (2) evaluate and treat for cardiovascular risk factors including hypertension, obesity, smoking, and dyslipidemia *(Class IIa; Level of Evidence C*).
Magee LA, Pels A, Helewa M, Rey E, von DP. Et al. **Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive**	**Diagnosis of Hypertension** • Hypertension in pregnancy should be defined as an office (or in-hospital) systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, based on the average of at least 2 measurements, taken at least 15 minutes apart, using the same arm. (II-2B). • Severe hypertension should be defined, in any setting, as a systolic blood pressure of ≥ 160 mmHg or a diastolic blood pressure of ≥ 110 mmHg based on the average of at least 2 measurements, taken at least 15 minutes apart, using the same

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summary. ***J Obstet Gynaecol Can* 2014;36(5):416-441.** **(selected)**	arm. (II-2B) **Measurement of Proteinuria** • All pregnant women should be assessed for proteinuria. (II-2B) Urinary dipstick testing (by visual or automated testing) may be used for screening for proteinuria when the suspicion of preeclampsia is low. (II-2B) • Significant proteinuria should be defined as ≥ 0.3 g/d in a complete 24-hour urine collection or ≥ 30 mg/mmol urinary creatinine in a spot (random) urine sample. (II-2B) • Significant proteinuria should be suspected when urinary dipstick proteinuria is ≥ 1+. (II-2A). More definitive testing for proteinuria (by urinary protein:creatinine ratio or 24-hour urine collection) is encouraged when there is a suspicion of preeclampsia, including: ≥ 1+ dipstick proteinuria in women with hypertension and rising blood pressure and in women with normal blood pressure, but symptoms or signs suggestive of preeclampsia. (II-2A) • Proteinuria testing does not need to be repeated once significant proteinuria of preeclampsia has been confirmed. (II-2A). There is insufficient information to make a recommendation about the accuracy of the urinary albumin:creatinine ratio. (II-2L) **Dietary and Lifestyle Changes** • There is insufficient evidence to make a recommendation about the usefulness of the following: new severe dietary salt restriction for women with any HDP, ongoing salt restriction among women with pre-existing hypertension, heart-healthy diet, and calorie restriction for obese women. (III-L). • There is insufficient evidence to make a recommendation about the usefulness of exercise, workload reduction, or stress reduction. (III-L). • For women with gestational hypertension (without preeclampsia), some bed rest in hospital (vs. unrestricted activity at home) may be useful to decrease severe hypertension and preterm birth. (I-B). • For women with preeclampsia who are hospitalized, strict bed rest is not recommended. (I-D). For all other women with an HDP, the evidence is insufficient to make a recommendation about the usefulness of some bed rest, which may nevertheless be advised based on practical considerations. (III-C) **Antihypertensive Therapy for Severe Hypertension Recommendations** • Blood pressure should be lowered to < 160 mmHg systolic and < 110 mmHg diastolic. (I-A). • Initial antihypertensive therapy in the hospital setting should be with nifedipine short-acting capsules, parenteral hydralazine, or parenteral labetalol. (I-A) (Table 7). • Alternative antihypertensive medications include a nitroglycerin infusion (I-B), oral methyldopa (I-B), oral labetalol (I-B), oral clonidine (III-B), or postpartum, oral captopril. (III-B). • Refractory hypertension may be treated with sodium nitroprusside. (III-B). • Nifedipine and magnesium sulphate can be used contemporaneously. (II-2B). • Magnesium sulphate is not recommended solely as an antihypertensive agent. (I-E) 68. Continuous fetal heart rate monitoring is advised until blood pressure is stable. (III-L)
Hypertension in Pregnancy. Report of the American College of Obstetricians & Gynecologists Task Force on Hypertension in	• Close monitoring of women with gestational hypertension or preeclampsia without severe features, with serial assessment of maternal symptoms and fetal movement (daily by the woman), serial measurements of BP (twice weekly), and assessment of platelet counts and liver enzymes (weekly) is suggested. • For women with mild gestational hypertension or preeclampsia with a persistent BP of less than 160 systolic or 110 diastolic, it is suggested that antihypertensive medications not be administered. For women with gestational hypertension

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Pregnancy ***Obstetrics & Gynecology* 2013:122:1122-31** **(selected)**	or preeclampsia without severe features, it is suggested that strict bed rest not be prescribed. • For women with preeclampsia with systolic BP of less than 160 and a diastolic BP less than 110 and no maternal symptoms, it is suggested that magnesium sulfate not be administered universally for the prevention of eclampsia. • For women with preeclampsia with severe hypertension during pregnancy (sustained systolic BP of at least 160 or diastolic of at least 110), the use of antihypertensive therapy is recommended.
5.1.3 Statin Use during Pregnancy	
Stone NJ, Robinson JG, Lichtenstein AH et al. **2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.** ***Circulation* 2014;129(25 Suppl 2):S1-45.**	Statins are listed as pregnancy category X and should not be used in women of childbearing potential unless these women are using effective contraception and are not nursing
5.1.4 Diabetes during Pregnancy	
Thompson D, Berger H, Feig D et al. **Canadian Diabetes Association Clinical Practice Guidelines Expert Committee Diabetes and pregnancy** ***Can J Diabetes* 2013;37 Suppl 1:S168-S183.** **(selected)**	**Pregestational Diabetes** **Management in pregnancy** Pregnant women with type 1 or type 2 diabetes should: a. Receive an individualized insulin regimen and glycemic targets typically using intensive insulin therapy [Grade A, Level 1B, for type 1; Grade A, Level 1, for type 2] b. Strive for target glucose values: Fasting PG <5.3 mmol/L; 1-hour postprandial <7.8 mmol/L; 2-hour postprandial <6.7 mmol/L [Grade D, Consensus]; c. Be prepared to raise these targets if needed because of the increased risk of severe hypoglycemia during pregnancy [Grade D, Consensus]; d. Perform SMBG, both pre- and postprandially, to achieve glycemic targets and improve pregnancy outcomes [Grade C, Level 3] Women with pregestational diabetes may use as part or lispro in pregnancy instead of regular insulin to improve glycemic control and reduce hypoglycemia [Grade C, Level 2, for as par; Grade C, Level 3, for lispro. Detemir [Grade C, Level 2] or glargine [Grade C, Level 3] may be used in women with pregestational diabetes as an alternative to NPH.

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	Intrapartum glucose management. Women should be closely monitored during labour and delivery, and maternal blood glucose levels should be kept between 4.0 and 7.0 mmol/L in order to minimize the risk of neonatal hypoglycemia [Grade D, Consensus]. Women should receive adequate glucose during labour in order to meet their high-energy requirements [Grade D, Consensus]. **Postpartum** Women with pregestational diabetes should be carefully monitored postpartum as they have a high risk of hypoglycemia [Grade D, Consensus]. Metformin and glyburide may be used during breastfeeding [Grade C, Level 3 for metformin; Grade D, Level 4, for glyburide]. Women with type 1 diabetes in pregnancy should be screened for postpartum thyroiditis with a TSH test at 6-8 weeks postpartum [Grade D, Consensus]. All women should be encouraged to breastfeed since this may reduce offspring obesity, especially in the setting of maternal obesity [Grade C, Level 3] **Gestational Diabetes** **Diagnosis** The preferred approach for the screening and diagnosis of GDM is the following [Grade D, Consensus]: a. Screening for GDM should be conducted using the 50 g GCT administered in the nonfasting state with PG glucose measured 1 hour later [Grade D, Level 4]. PG 7.8 mmol/L at 1 hour will be considered a positive screen and will be an indication to proceed to the 75 g OGTT [Grade C, Level 2]. PG 11.1 mmol/L can be considered diagnostic of gestational diabetes and does not require a 75 g OGTT for confirmation [Grade C, Level 3]. b. If the GCT screen is positive, a 75 g OGTT should be performed as the diagnostic test for GDM using the following criteria: ≥1 of the following values: Fasting ≥5.3 mmol/L 1 hour ≥10.6 mmol/L 2 hours ≥9.0 mmol/L [Grade B, Level 1]. Management during pregnancy 20. Women with GDM should: a. Strive for target glucose values: i. Fasting PG Fasting PG <5.3 mmol/L [Grade B, Level 2]; ii. 1-hour postprandial <7.8 mmol/L [Grade B, Level 2], iii. 2-hour postprandial <6.7 mmol/L [Grade B, Level 2]; b. Perform SMBG, both fasting and postprandially, to achieve glycemic targets and improve pregnancy outcomes [Grade B, Level 2] If women with GDM do not achieve glycemic targets within 2 weeks from nutritional therapy alone, insulin therapy should be initiated [Grade D, Consensus]. Insulin therapy in the form of multiple injections should be used [Grade A, Level 1]

Evidence Tables

Antithrombotics Use during Pregnancy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Antiplatelets (Aspirin)					
Helms et al. 2008 **USA** **Survey**	NA	NA	A survey was sent to 384 US practicing members of the American Academy of Neurology Stroke and Vascular Neurology section, which included 2 questions related to their treatment of pregnant women during the first trimester with a previous history of noncardioembolic stroke related to pregnancy and the same question related to ischemic stroke prophylaxis for a previous stroke not related to pregnancy.	Response options included: No treatment, aspirin (81 and 325 mg), clopidogrel (75 mg), ASA/dipyridamole, warfarin, UFH, LMWH and other	The response rate was 60% (230 respondents). Treatment preferences for stroke prophylaxis in women with a previous nonpregnancy-related stroke were: 81 mg ASA: 42% No treatment: 24% Other: 8% 325 mg aspirin: 8% LMWH:6% Clopidogrel: 5% UFH, ASA/dipyridamole and warfarin: <5% Treatment preferences for stroke prophylaxis in women with a previous pregnancy-related stroke were: 81 mg ASA: 34% LMWH: 24% No treatment: 12% Other: 9% 325 mg aspirin: 7% UFH: 6% Clopidogrel, ASA/dipyridamole and warfarin: <5%
Nørgard et al. 2005 **Denmark** **Retrospective study**	NA	3,415 children included in the Hungarian Congenital Abnormality Registry with 4 congenital abnormalities of interest, and a reference group, composed of 19,428 children with other congenital abnormalities.	The association between maternal aspirin use between 5-12 weeks of gestation and congenital abnormalities was examined. Aspirin exposure was obtained using a detailed questionnaire, and the logbooks of treating obstetricians.	Neural-tube defects, exomphalos/gastroschisis, cleft lip or palate and posterior cleft palate Analyses were adjusted for maternal age, parity, folic acid use during 1st trimester, nausea/vomiting or cold symptoms during 1st trimester and presence of diabetes or epilepsy	The odds of any of the 4 congenital abnormalities associated with aspirin exposure was not significantly increased relative to the reference group (272/19,428 (1.4%); RR=1.00) Neural-tube defects: 25/1,202 cases (2.1%); OR=1.1, 95% CI 07.-1.6 Exomphalos/gastroschisis: 3/238 cases (1.3%); OR=0.7, 95% CI 0.2-2.2 Cleft lip ± palate: 28/1,374 cases (2.0%); OR=0.9, 95% CI 0.6-1.3 Posterior cleft palate: 12/601 cases (2.0%);

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					OR=1.0, 95% CI 0.6-1.8
Kozer et al. 2002 **Canada** **Meta-analysis**	NA	22 controlled studies with sample sixes ≥6 including women who had been exposed to aspirin during the first trimester of pregnancy and reported on congenital malformations.	The association between maternal exposure to aspirin and congenital abnormalities was examined. Aspirin exposure was established based on prescriptions, doctors' and medical records, questionnaires or interviewed conducted with the mothers. Outcomes were established by hospital records, and databases/registries of congenital malformations	CNS defects, congenital heart defects, and gastroschisis	The overall rate of congenital malformations was not significantly higher in the aspirin-exposed group (5.5% vs. 3.9%, OR=1.33, 95% CI 0.94-1.89, p=0.11). Results from 8 studies included. The incidence of CNS defects was not significantly higher in the aspirin-exposed group (OR=1.39, 95% CI 0.89-2.16). Results from 3 studies included. The incidence of cardiac malformations was not significantly higher in the aspirin-exposed group (3.4% vs. 5.4%, OR=1.01, 95% CI 0.91-1.12, p=0.80). Results from 6 studies included. The incidence of gastroschisis was significantly higher in the aspirin-exposed group (OR=2.37, 95% CI 1.44-3.88, p=0.0006). Results from 5 studies included.
Anticoagulation					
Xu et al. 2016 **China** **Systematic review & Meta-analysis**	NA	51 studies (2,113 pregnancies) including pregnant women who received anticoagulation therapy related to management of mechanical heart valves.	4 regimens were defined: i) vitamin K antagonist (VKA) taken throughout pregnancy (n=37), with a low dose sub group of ≤ 5 mg/d or less; ii) heparin (H)/VKA regimen using VKAs except for unfractionated heparin (UFH) or low molecular weight heparin (LMWH) during 6-12 weeks of pregnancy (n=13); iii) adjusted dose LMWH taken throughout pregnancy (n=12); and iv) adjusted dose UFH taken throughout pregnancy (n=8).	**Primary outcomes:** Maternal major thrombotic events, maternal deaths and fetal wastage **Secondary outcomes:** Major antenatal hemorrhage events (MAHE), and congenital fetal anomaly (CFA).	The frequencies of a major thrombotic event were: VKA:2.8% (low-dose sub group 1.1%); H/VKA: 7.4%; LMWH: 4.4%; UFH:29.9% The frequencies of MAHEs were: VKA:0.49% (low-dose sub group 0.68%); H/VKA: 0.61%; LMWH: 4.1%; UFH:5.3% The frequencies of a maternal deaths were: VKA:0.89% (low-dose sub group 0.31%); H/VKA: 0.86%; LMWH: 1.8%; UFH:0.88% The frequencies of fetal wastage were: VKA: 32.5% (low-dose sub group 19.2%); H/VKA: 22.7%; LMWH: 12.2%; UFH: 53.6%. *Comparisons between regimens* **High vs. low dose VKA**: High dose VKAs were associated with higher incidence of fetal wastage (19.2% vs. 63.95, p<0.0001) and warfarin embryopathy (0.45% vs. 8.3%, p<0.0001). There were no significant differences between groups for

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					the outcomes of maternal death, major thrombotic events or MAHEs. **H/VKA vs. LMWH:** There were no significant differences between groups in the incidences of: maternal deaths (0.86% vs. 1.77%, p=0.77), major thromboembolic events (7.4% vs. 4.4%, p=0.38), or CFA (0.74% vs. 05, p=0.89%). H/VKA use was associated with significantly higher incidences of fetal wastage (22.7% vs. 12.2%, p=0.024%) and spontaneous abortion (12.7% vs. 5.1%, p=0.036). **Low-dose VKA vs. H/VKA**: There were no significant differences between groups in the incidences of maternal deaths (0.31% vs. 0.86%, p=0.66), MAHE (0.68% vs. 0.61%, p=1.00), fetal wastage (19.2% vs. 22.7%, p=0.25) or spontaneous abortions (15.1% vs. 12.7%, p=0.42). There were significantly more cases of major thromboembolic events in the H/VKA group (7.4 vs. 1.1, p<0.001). *Pooled analyses* Compared with H/VKA the odds of fetal wastage were not significantly higher compared with low-dose VKA (OR=0.79, 95% CI 0.47-1.34, p=0.38). Results from 4 studies included Compared with H/VKA, the odds of major thromboembolic events were significantly lower for the VKA regimen (OR=0.36, 95% CI 0.15-0.86, p=0.02). Results from 3 studies included.
Rodger et al. 2014 **Canada** **RCT** ***Thrombophilia in Pregnancy Prophylaxis Study (TIPPS)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	292 pregnant women recruited from 36 centres with confirmed thrombophilia at high-risk of placenta-mediated pregnancy, pregnancy loss, complications and/or DVT. Women were excluded if they were ≥21 weeks' gestation or had known	Women were randomized to receive antepartum dalteparin (5,000 IU) once daily from randomization to 20 weeks' gestation and then the same dose twice daily until 37 weeks of gestation vs. no dalteparin. All women received 5,000 IU	**Primary outcome:** Composite including any of: proximal DVT, PE or sudden maternal death, severe or early onset preeclampsia, oliguria, pulmonary edema, coagulopathy, birth of small-for-gestational-age (SGA) infant, or pregnancy loss. **Secondary outcomes:**	The primary outcome occurred in 25 women in the dalteparin group and 27 women in the control group (17.1% vs. 18.9%, risk difference of -1.8%, 95% CI -10.6%-7.1%, p=0.70). There were no significant interactions for the primary outcome found for pre-planned subgroup analysis including age, previous history loss, previous preeclampsia, previous SGA infant, previous VTE, thrombophilia, and aspirin use.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		contraindications to heparin. Mean maternal age was 32 years. Mean gestational age at randomization was 12 weeks. Mean of 2.2 previous pregnancies, 1.0 deliveries, with 61% of women experiencing pregnancy-related complications	dalteparin once daily postpartum until day 42.	Major and minor bleeding events.	There was no significant differences in the incidence of any of the individual components of the primary outcome (major VTE: 0.7% vs. 1.4%, risk difference of -0.7%, 95% CI -3.1%-1.6%, p=0.62; preeclampsia: 5.5% vs. 3.3%, risk difference of 2.0%, 95% CI -2.8%-6.8%, p=0.42; severe or early onset preeclampsia: 4.8% vs. 2.8%, risk difference of 2.0%, 95% CI -2.4%-6.4%, p=0.38; SGA infant: 6.2% vs. 8.4%, risk difference of -2.2%, 95% CI -8.2%-3.8%, p=0.47; any pregnancy loss: 8.2% vs. 7.0%, 95% CI 1.2%, 95% CI-4.9%-7.3%, p=0.69). There was no significant difference in the incidence of major bleeding between groups (2.1% vs. 1.45, RD=0.7%, 95% CI -2.4%-3.7%, p=1.0), but the incidence of minor bleeding events was significantly higher in the dalteparin group (19.6% vs. 9.2%, RD=10.4%, 95% CI 2.3%-18.4%, p=0.01).
Singh et al. 2013 **India** **Retrospective study**	NA	55 women who received the low molecular weight heparin (LMWH) enoxaparin and delivered at a single hospital. Mean age was 26 years.	Review of the medical records of all women who received a LMWH for any indication	Maternal and fetal outcomes	40 women received LMWH in the antepartum and postpartum period, 12 women received LMWH in the antepartum period and 3, in the postpartum period only. Dose was 1 mg/kg once or twice daily. The most common indication for LMWH use was heart disease (60%) for valvular heart disease, with valve replacement, atrial fibrillation or thrombus. Other indications included chronic DVT (7%), thrombophilias (9.1%0, pregnancy loss (18%) and prophylaxis for DVT (5.5%). There were 49 live births (mean period of gestation was 37 weeks), 4 abortions and 1 stillbirth. 4 births were premature There were 6 cases of intrauterine growth restriction and 1 case each of, preeclampsia, gestational HTN and placenta abruption. No babies were born with congenital malformations.
Visser et al.	Concealed	207 women aged 18-41	Before the 7th week of	**Primary outcome:**	The trial was stopped prematurely due to slow

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
2011 **Finland** **RCT** ***Low Molecular Weight Heparin and/or Aspirin in Prevention of Habitual Abortion (HABENOX)***	Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	years with recurrent miscarriage (≥3 during 1st trimester, ≥2 during 2nd trimester or one 3rd trimester fetal loss combined with one 1st trimester miscarriage) with one positive thrombophilia test conducted before pregnancy (F V Leiden (heterozygote) or protein C or S deficiency, or anticardiolipin antibodies (low to moderate level), prothrombin gene mutation, or high level of F VIII.) Mean maternal age was 32 years.	gestation, women were randomized to one of three groups: i) 40 mg enoxaparin daily + placebo; (n=68); ii) 40 mg enoxaparin + 100 mg aspirin daily (n=63) and 100 mg aspirin daily, used as the control group (n=76). Aspirin and placebo were discontinued at 36 weeks. Enoxaparin was continued until labour.	Live birth after 24 weeks' gestation **Secondary outcomes:** Preeclampsia, placental abruption, premature delivery, and intrauterine growth restriction, bleeding complications	recruitment. 270 participants planned. Based on a second thrombophilia test conducted at 12 weeks' gestation (i.e after inclusion into study), the abnormality was confirmed in 24.6% of women. The number of live births in each group was 71%, RR=1.17, 95% CI 0.92-1.48 for enoxaparin + placebo and 65%, RR=1.08, 95% CI 0.83-1.39 for enoxaparin + aspirin, compared with aspirin (61%). In sub group analysis, the number of live births was not significantly elevated, based on age, confirmed thrombophilia, and timing or number of previous miscarriages, in women in either of the 2 active treatment groups, relative to the control group. There were no significant differences between the groups in terms of any of the secondary outcomes. There were 4 cases of preeclampsia, a case of placental abruption, 14 cases of premature delivery and 9 cases of intrauterine growth restriction. The number of bleeding complications did not differ significantly among study groups.
Chan et al. 2000 **USA** **Systematic review**	NA	28 studies representing 976 women (1,234 pregnancies) with mechanical heart valves who were on a defined anticoagulation regimen.	3 regimens were defined: Oral anticoagulants (OA) taken throughout pregnancy, replacing OAs with heparin during the first trimester and heparin, taking throughout pregnancy. The frequencies of the outcomes of interest were pooled.	**Maternal outcomes:** Major bleeding, thromboembolic complications and death **Fetal outcomes:** Spontaneous abortions, congenital fetal anomalies	**Maternal outcomes** Total maternal mortality was 2.9% (1.8% regimen 1; 4.2% regimen 2; 15% regimen 3) Total thromboembolic events were 24.3% (3.9% regimen 1; 9.2% regimen 2; 33.3% regimen 3). The pooled frequency of major maternal bleeding was 2.5%. **Fetal outcomes** The frequencies of congenital abnormalities were 6.4% (regimen 1); 3.4% (regimen 2) and 0% (regimen 3). The frequencies of spontaneous abortions were 24.7% (regimen 1); 24.8% (regimen 2) and 23.8%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					(regimen 3).
Greer & Nelson-Piercy 2005 **UK** **Systematic review**	NA	64 studies reporting on 2,777 pregnancies in which LMWH was primarily used for treatment of VTE, for thromboprophylaxis, or to prevent recurrent pregnancy loss (RPL) or other adverse pregnancy outcomes.	The safety and efficacy of LMWHs for thromboprophylaxis and treatment of venous thromboembolism (VTE) in pregnancy, was assessed.	**Primary outcome:** DVT, PE, other VTE, or arterial thrombotic events **Secondary outcomes:** Antenatal bleeding, postpartum hemorrhage, wound hematomas, allergic skin reactions, thrombocytopenia and pregnancy outcome	The most common indications for the use of LMWH were: Treatment of VTE (174 pregnancies), thromboprophylaxis (1,321 pregnancies), prevention of RPL (447 pregnancies), and unspecified prophylaxis (720 pregnancies). There were no maternal deaths. VTE and arterial thrombosis (associated with antiphospholipid syndrome) were reported in 0.86% (95% CI, 0.55%-1.28%) and 0.50% (95% CI, 0.28%-0.84%) of pregnancies, respectively. Significant bleeding was reported in 1.98% (95% CI, 1.50%-2.57%) of pregnancies. There were no cases of heparin-induced thrombocytopenia and thrombocytopenia, unrelated to LMWH, occurred in 0.11% (95% CI, 0.02%-0.32%) of pregnancies. Overall, live births were reported in 94.7% of pregnancies, including 85.4% in those receiving LMWH for recurrent pregnancy loss.
Safety of Acetaminophen (for pain relief)					
Liew et al. 2014 **USA** **Retrospective study**	NA	64,322 children of mothers, included in the Danish National Birth Cohort who had taken acetaminophen during weeks 6-12 weeks' gestation from 1996-2002.	Acetaminophen use was obtained by telephone questionnaires at 12th, 30th weeks gestation and 6 months after birth. Parental reports of Attention-deficit/hyperactivity disorder (ADHD) at 7 years were assessed using the Strengths and Difficulties Questionnaire. Records of prescription medications for ADHD	**Primary outcome:** Attention-deficit/hyperactivity disorder (ADHD) at 7 years (Strengths and Difficulties Questionnaire), hyperkinetic disorders (HKD)	56% of women reported ever using acetaminophen during pregnancy. The risk of a total score of ≥17 on the SDQ was significantly higher for women who used acetaminophen during pregnancy, after adjusting for potential confounders (RR=1.13, 95% CI 1.01-1.27). The risk was not increased significantly for women who had used acetaminophen **only** during the 1st, 2nd or 3rd trimester, but was increased for use in both the 2nd and 3rd trimesters, and all 3 trimesters. The risk of ADHD (using medication records) was increased significantly for women who had used

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			were also used A diagnosis of Hyperkinetic disorders (HKD) was confirmed by the Danish National Hospital Registry or the Danish Psychiatric Central Registry. The association between acetaminophen use and ADHD/HKD was examined.		acetaminophen during pregnancy, after adjusting for potential confounders (RR=1.29 95% CI 1.15-1.44). The risk of HKD (using hospital diagnosis) was increased significantly for women who had used acetaminophen during pregnancy, after adjusting for potential confounders (RR=1.37, 95% CI 1.19-1.59). The risk was increased significantly for women who had used acetaminophen only during the 1st trimester, and when used in the 1st and 3rd trimester, and all 3 trimesters.
Use of Aspirin for Prevention of Pregnancy Complications					
Rolnik et al. 2017 **UK** **RCT** ***The Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	Women, aged ≥18 years, with a singleton pregnancy with live fetus at the time that scanning, which was performed at 11 to 13 weeks of gestation, in women with a high risk (>1 in 100) for preterm preeclampsia according to the screening algorithm. Median gestation age at randomization was 12.7 weeks, median maternal age was 31.5 years. 67% of women were nulliparous	Women were randomized to receive 150 mg per day (n=878) or placebo (n=898), initiated from 11 to 14 weeks of gestation until 36 weeks of gestation.	**Primary outcome:** Delivery with preeclampsia before 37 weeks of gestation **Secondary outcomes**: Adverse outcomes of pregnancy before 34 weeks of gestation, before 37 weeks of gestation, and at or after 37 weeks of gestation (preeclampsia, gestational hypertension, small-for-gestational-age status without preeclampsia, miscarriage or stillbirth without preeclampsia, abruption without preeclampsia, Spontaneous delivery without preeclampsia) ; stillbirth or neonatal death; death and neonatal complications; neonatal therapy; and poor fetal growth	The odds of the primary outcome were significantly lower in the aspirin group (1.6% vs. 4.3%, OR=0.38, 95% CI 0.20-0.74, p=0.04). There was no significant between-group difference in the incidence of any secondary outcomes. Serious adverse events occurred in 1.6% of women in the aspirin group and 3.2%, in the placebo group.
Roberge et al. 2016	NA	3 RCTs (n=3,293) that recruited >350 women before 17 weeks'	Low aspirin (60 mg) for the prevention of preeclampsia or small-	Preeclampsia, severe preeclampsia and small- for-gestational- age (SGA)	Low-dose aspirin did not significantly reduce the risk of preeclampsia (RR=0.93, 95% CI 0.75-1.15), severe preeclampsia (RR=0.96, 95% CI 0.71-1.28),

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Canada **Meta-analysis**		gestation. Treatment was initiated from 12-32 (n=1) and 13-26 weeks (n=2) of pregnancy.	for-gestational-age neonates vs. placebo in high-risk women.	neonates	delivery of SGA neonate (RR=0.84, 95% CI 0.56-1.26) or pre-term birth (RR=0.92, 95% CI 0.76-1.12). Low-dose aspirin did not reduce the risk of any of the outcomes when initiated >16 weeks of gestation.
Schisterman et al. 2014 **USA** **RCT** ***Effects of Aspirin in Gestation and Reproduction (EAGeR)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	1,128 women, aged 18-40 years, attempting to become pregnant with a history of a single pregnancy loss (original stratum) or 1-2 previous pregnancy losses (expanded stratum), were recruited from 4 medical centres from 2005-2011.	Participants were randomized 1:1 to receive low-dose (n=81 mg) aspirin daily or placebo for 6 menstrual cycles, or until 36 weeks' gestation for women who became pregnant. Women in both groups also received 400 µg folic acid daily.	**Primary outcome:** Live births **Secondary outcomes:** Implantation, confirmed pregnancy, pregnancy loss (<20 weeks' gestation) and serious obstetric complications, and safety outcomes	Overall, the number of live births in the aspirin group was 309 (58%) vs. 286 (53%) in the placebo group. The difference between the groups was not significantly different (absolute difference in livebirth rate=5.09, 95% CI -0.84-11.02, p=0.098). When analysis was restricted to 242 women in the original stratum, there were significantly more live births in the aspirin group (62% vs. 53%, RR=1.13, 95% CI 1.01-1.37, p=0.045). Significantly more women in the aspirin group had a confirmed pregnancy (74% vs. 67%, RR=1.10, 95% CI 1.02-1.19, p=0.016), based on a positive urine test. There was no difference between groups in the number of pregnancy losses (13% vs. 12%, RR=1.06, 95% CI 0.77-1.46, p=0.78). There were no significant differences between groups on any of the other secondary outcomes or safety outcomes. There were no major birth defects in either group, and 8 minor defects (4 in each group). 15% of women in the aspirin group were non-compliant with medication vs. 13% in placebo group.

ITT: intention-to-treat

Blood Pressure Management

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Increased Risk of Stroke Associated with Pregnancy-related Hypertension					
Leffert et al. 2015 **USA** **Retrospective study**	NA	81,983,216 pregnancy-related admissions from 1994-2011 of women aged 15-44 years from the Nationwide Inpatient Sample	Hospitalizations for hypertensive disorders of pregnancy were identified as were admissions for stroke. Multivariable logistic regression was used to assess the effect of hypertensive disorders of pregnancy plus comorbid conditions, adjusting for age, race–ethnicity, delivery mode, payer, hospital region, hospital teaching status, and study interval and to investigate the effect of hypertensive disorders of pregnancy on stroke-related complications, including mechanical ventilation, seizure, pneumonia, prolonged hospital stay, and death during hospitalization.	Temporal trends in hypertensive disorders of pregnancy; and increased risks of stroke-related complications among women with hypertensive disorders of pregnancy-compared with pregnancy-associated stroke without hypertensive disorders.	There were 31,673 hospitalizations for stroke (3.8/10,000 pregnancy-related hospitalization), of which 31.2% (9,890) occurred in patients with hypertensive disorders of pregnancy. The stroke rate for hypertensive-related pregnancy increased from 0.8 to 1.6/10,000 pregnancy hospitalizations over the study period (103% increase), compared with an increase of 2.2 to 3.2/10,000 (47%) hospitalizations for women without hypertension-related pregnancy. Women with hypertensive-disorders of pregnancy were 5.2 times more likely to have a stroke (95% CI 4.9-5.6). The majority of stroke occurred outside the delivery period (32% antenatal, 34% postpartum). Among women with hypertensive-disorders of pregnancy, those with traditional risk factors were at significantly increased risk of stroke (e.g., congenital heart disease: adj OR=13.1, 95% CI 9.1-18.9; atrial fibrillation: adj OR=8.1, 95% CI4.4-14.9; primary thrombocytopenia: adj OR=5.50, 95% CI 3.1-9.9). The frequency of stroke-related complications was higher among women with hypertensive disorders of pregnancy (e.g., need for mechanical ventilation; adj OR=1.93, 95% CI 1.63-2.25; pneumonia: adj OR=1.78, 95% CI 1.26-2.51; seizure: adj OR=1.29, 95% CI 1.08-1.55).
James et al. 2005 **USA** **Retrospective study**	NA	2,850 women, included in the Nationwide Inpatient Sample from 2000-2001, who had been discharged from one of 1,000 hospitals with a pregnancy-related stroke diagnosis (707 hemorrhagic stroke, 766	Medical records were reviewed. Non-adjusted models for pregnancy-related stroke risk and medical conditions and complications of pregnancy/delivery, were estimated.	Stroke	Overall, pregnancy-related stroke risk was 34.2 (95% CI 33.3-35.1)/ 100,000 pregnancies. The odds of stroke were significantly increased for women with hypertension (OR=6.1, 95% CI 4.5-8.1).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		ischemic stroke, 50 cerebral vein thrombosis and 1,327 pregnancy-related cerebrovascular events)			
Lanska & Kryscio 1998 **USA** **Retrospective study**	NA	85 women aged 15-44 years sampled from US National Hospital Discharge Survey (1979-1991) that included short-stays in non-federal hospitals. Women that experienced a stroke during pregnancy, birth or the postpartum period were included.	Risks of stroke events were estimated. Multivariable models were built, adjusting for potential confounders, to identify independent predictors of stroke. Variables of interest included maternal age, race, HTN, census region, hospital ownership and number of hospital beds.	Stroke incidence and risk factors	The estimates of the total number of strokes in the US during the study period, among 50,264,631 deliveries, were 8,918 strokes and 5,723 cases of intracranial venous thrombosis. The associated risk per 100,000 deliveries were 17.7 (stroke), 11.4 (intracranial venous thrombosis) and 29.1 (total). The total number of strokes in the sample during the study period, among 281,116 women were 54 strokes and 31 cases of intracranial venous thrombosis. The associated risk per 100,000 deliveries were 19.2 (stroke), 11.0 (intracranial venous thrombosis) and 30.2 (total). 24 strokes occurred antepartum, 30 occurred postpartum and the timing of stroke was unknown in the remaining 16 cases HTN was an independent predictor of stroke, but not for venous thrombosis Stroke: OR=8.83, 95% CI 4.82-16.18 Intracranial venous thrombosis: OR=0.64, 95% CI 0.08-5.23 Combined events: OR=5.13, 95% CI 2.97-8.85
Treatment of Mild to Moderate Hypertension in Pregnancy					
Magee et al. 2015 **Canada** **RCT** ***Control of Hypertension In Pregnancy Study (CHIPS)***	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	1,030 women from 111 centres in 16 countries, gestational age 14-33+6 weeks, with nonproteinuric, pre-existing or gestational hypertension (pre-existing hypertension: DBP ≥ 90 mmHg before pregnancy or 20 weeks' gestation; gestational hypertension:DBP ≥ 90	Women were randomized to 'tight' BP control (n=490) using antihypertensive agents, as necessary with a DBP goal of ≤85 mmHg vs. "less tight" (n=497) with a DBP goal of ≤ 100 mmHg, for the duration of their pregnancy. The recommended first-line agent was labetalol. ACE	**Primary outcome:** Composite of pregnancy loss or need for high-level neonatal care (>48 hours for 28 days or until discharge home) **Secondary outcome:** Serious maternal complications occurring up to 6 weeks postpartum (or until discharge, if	The median duration of study participation was 12.1 weeks. The frequency of the primary outcome was not significantly lower among women in the tight-control group (30.7% vs. 31.4%, adj OR=1.02, 95%CI 0.77-1.35). There were no significant differences between groups in the frequency of any of individual component of the primary outcome (miscarriage, ectopic pregnancy, elective termination, perinatal death, still birth or high-

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		mmHg that developed> 20 weeks) and DBP of 90 - 105 mmHg if not taking antihypertensive therapy, or DBP of 85- 105 mmHg if taking antihypertensive therapy. Women with severe systolic HTN were excluded. Mean age was 34 years. Mean weeks of gestation at randomization was 24.8. 75% of women had pre-existing HTN. 57% were taking antihypertensive agents at enrollment.	inhibitors, ARBs, direct renin inhibitors and atenolol were not permitted	longer), including death, stroke, eclampsia, blindness, uncontrolled HTN, use of inotropic agents, pulmonary edema, respiratory failure, MI, hepatic dysfunction, hepatic hematoma or rupture, renal failure, and transfusion.	level neonatal care). The frequency of serious maternal complications was not significantly lower among women in the tight-control group (2.0% vs. 3.7%, adj OR=1.74, 95% CI 0.79-3.84). There was a single stroke/TIA in the tight-control group vs. 0 in the less-tight control group. The frequency of severe HTN was significantly higher among women in the less-tight control group (40.6% vs. 27.5%, adj OR=1.80, 95% CI 1.34-2.37).
Abalos et al. 2013 **South Africa** **Cochrane Review**	NA	48 RCTs (4,723 women) evaluating any antihypertensive drug treatment for mild to moderate hypertension during pregnancy. HTN was defined as SBP 140-169 mmHg and DBP 90-109 mmHg	RCTs comparing ≥1 antihypertensive drug vs. either placebo or no antihypertensive drug (n=29) and comparisons of one antihypertensive drug vs. another (n=22). Duration of treatment was at least 7 days. The antihypertensive drugs used in these trials included: alpha agonists (methyldopa), beta blockers (acebutolol, atenolol, labetalol, mepindolol, metoprolol, pindolol, oxprenolol and propranolol), calcium channel blockers (isradipine, nicardipine, nifedipine, nimodipine and verapamil), vasodilators (hydralazine	**Primary outcome:** Severe HTN, proteinuria, any reported baby death, small-for-gestational age, preterm birth **Secondary outcomes:** Severe preeclampsia, eclampsia, HELLP syndrome,	**Any antihypertensive drug vs. none** The risk of severe HTN was significantly reduced in the active treatment group. RR= 0.49, 95% CI 0.40-0.60, p<0.0001. Results from 20 trials (2,558 women included. The risk of pre-eclampsia/proteinuria was not significantly reduced in the active treatment group. RR= 0.93, 95% CI 0.80-1.08, p=0.34. Results from 23 trials (2,851 women) included; however, in the sub group examination of beta blockers (vs. no treatment), the risk of developing proteinuria/pre-eclampsia was significantly reduced. RR=0.73, 95% CI 0.57-0.94. Results from 8 trials (883 women), included. The risk of fetal or neonatal death, pre-term birth or small-for-gestational age were not significantly reduced for women taking antihypertensive treatment **Any antihypertensive vs. methyldopa** The risk of severe HTN was significantly reduced with other antihypertensive agents, compared with methyldopa. RR= 0.54, 95% CI 0.30-0.95, p<0.0001. Results from 11 trials (638 women) included.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			and prazozin), ketanserin and glyceryl trinitrate.		The risk of proteinuria/eclampsia was significantly reduced with beta blockers or calcium channel blockers use compared with methyldopa. RR=0.73, 95%CI 0.54-0.99. Results from 11 trials (997 women) were included.
Nabhan & Elsedawy 2011 **Egypt** **Cochrane Review**	NA	2 RCTs (265 pregnant women) with mild or moderate pre-existing or non-proteinuric gestational hypertension. Mild HTN was defined as SBP of 140-159 mmHg and a DBP of 90- 99 mmHg; moderate HTN was defined as BPs of 160-169/100-109 mmHg, or as defined by study authors.	Women were randomized to tight vs. very tight control of mild-moderate, preexisting or non-proteinuric gestational hypertension. Antihypertensive agents used were methyldopa (n=1) and was labetalol (n=1). The target blood pressures were 100 mmHg for the less tight group and 85 mmHg for the tight group (n=1) and target BP of 130-139/80-89 mmHg vs. <130/80 mmHg (n=1).	**Primary outcome:** Severe pre-eclampsia, eclampsia, maternal death, perinatal deaths **Secondary outcomes:** Antenatal hospitalization, maternal admission to ICU, women's satisfaction, additional drugs to achieve control. Increase in dose of antihypertensive drugs to achieve control, gestational age at delivery, rate of induction of labor, rate of cesarean delivery, placental abruption, fetal distress, fetal growth restriction, birthweight, Apgar score <7 at one minute, admission to neonatal ICU.	The risk of any of the primary outcomes was not significantly increased in patients in the tight control group Severe preeclampsia: RR=1.28, 95% CI 0.97-1.70, p=0.08. Perinatal death: RR=1.48, 95% CI 0.25-8.74 There were no cases of eclampsia, maternal death or stroke The risk of all but one of the secondary outcomes was not significant increased among patients in the tight control group. More women in the tight control group were group were hospitalized during their pregnancy (RR= 2.53, 95% CI 1.14-5.63, p=0.023. The results from a single trial were included (n=125 participants)
Prevention of Hypertensive Disorders of Pregnancy					
Hofmeyr et al. 2014 **UK** **Cochrane review**	NA	13 RCTs (n=15, 730) pregnant women < 35 weeks of gestation, regardless of their risk of hypertensive disorders of pregnancy. Women with diagnosed hypertensive disorders of pregnancy were excluded.	Women were randomized to receive either high-dose (≥1 g/day, n=14) or low-dose (<1 g/day, n=10) calcium supplement or placebo, until delivery. Six of the low-dose studies included a co-intervention (vit D, linoleic acid or antioxidants)	**Primary outcome:** High blood pressure (with or without proteinuria), defined as DBP≥ 90 mmHg, an increase in SBP of ≥30 mmHg or in DBP of ≥15 mmHg, high blood pressure with significant proteinuria **Secondary outcomes:**	High-dose Ca supplementation was associated with a significantly reduced risk of high blood pressure (RR= 0.65, 95% CI 0.53-0.81, p<0.0001). The results of 12 trials were included. High-dose Ca supplementation was associated with a significantly reduced risk of pre-eclampsia (RR= 0.45, 95% CI 0.31-0.65, p<0.0001). The results of 13 trials were included. The effect was most pronounced for women with low Ca intakes (RR=0.36, 95% CI 0.20-0.65) and for women at high risk of pre-eclampsia

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				Maternal death or serious morbidity, placental abruption, caesarean section, severe pre-eclampsia or LOS ≥7 days	(RR= 0.22, 95% CI 0.12-0.42). Low-dose Ca supplementation was associated with a significantly reduced risk of high blood pressure (RR= 0.53, 95% CI 0.38-0.74, p<0.0001). The results of 5 trials were included.

Safety of Statin Use during Pregnancy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Karalis et al. 2016 **USA** **Systematic review & meta-analysis**	NA	16 studies examining the relationship between stain exposure during the first trimester and birth defects (5 case series, 3 cohort studies, 3 registry-based studies, 1 RCT and 4 systematic reviews)	Narrative synthesis, group by study type	**Primary outcome:** Congenital abnormalities	There was some suggestion of an increased risk of fetal abnormalities from earlier case series. In later-published cohort and registry-based studies included that controlled for confounding risk factors such as diabetes and obesity, there was no evidence of any relationship with statin exposure in pregnancy and congenital anomalies.
Bateman et al. 2015 **USA** **Retrospective study**	NA	Women aged 12-55 years with completed pregnancies. The cohort was assembled using a Medicaid database that was linked to live born infants (2000-2007)	The outcomes of women who had taken a statin during pregnancy (n=1,152) were compared with women who had not (885,844). A propensity score matching method was used to account for baseline differences between groups (stain users n=1,109, no statin n=3,327).	**Primary outcome:** Congenital malformations, organ specific malformations	In the full cohort, the incidence of major congenital malformations was 6.34% for statin users compared with 3.55% for non-statin users (unadjusted RR=1.79, 95% CI 1.43-2.23). In the analysis using propensity scores, the risk of major malformations was not significantly increased (RR=1.07, 95% CI 0.85-1.37). Using propensity scores, there were no significant increases in the risk of any organ specific malformations including those of the central nervous system, cardiac malformations, respiratory malformations, cleft palate/lip, GI malformations, genitourinary malformations, or MSK malformations. Estimated risks in sensitivity and sub groups analyses were similar to those of the primary analysis
Zarek & Koren	NA	6 controlled studies	The outcomes of women	**Primary outcome:**	The use of statins during pregnancy was not

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
2014 **Canada** **Systematic review & meta-analysis**		(n=618 participants) examining pregnant women exposed to statins	who were exposed to statins were compared to those who were not	Birth defects **Secondary outcome:** Miscarriages	associated with an increased risk of birth defects (RR=1.15, 95% CI 0.75-1.76, p=0.52). The use of statins was associated with an increased risk of miscarriage (RR=1.35, 95% CI 1.04-1.75)
Winterfeld et al. 2013 **Germany** **Case-control study**	NA	249 women who contacted (or whose physician contacted) one of 11 Teratological Information Services seeking advice about statin therapy during the 1st trimester of pregnancy from 1990-2009. Median maternal age was 33 years. 249 women who made enquiries to the same agency requesting advice on agents known to be nonteratogenic. Median maternal age was 32 years.	Details of the pregnancy outcome were obtained through a structured telephone interview or mailed questionnaire during the neonatal period and were compared with those from the control group, adjusting for potential confounders include maternal age, ETOH consumption, smoking status, number of previous elective terminations and gestational age.	**Primary outcome:** Major birth defects **Secondary outcomes:** Lives births, miscarriages, pregnancy terminations preterm deliveries and gestational age and birthweight at delivery	A higher proportion of women in the statin-exposed group reported tobacco use (17.6% versus 8.7%). The median gestational age at initial contact was 1 week earlier in the statin-exposed group (8 vs. 9 weeks). Simvastatin was the most commonly used agent (n=124), followed by atorvastatin (n = 67), pravastatin (n = 32), rosuvastatin (n = 18), fluvastatin (n = 7), and cerivastatin (n = 1). Therapy was started before conception in 89% of exposed women. Approximately half of the women (48%) continued statin treatment beyond week 5 of gestation and 21% beyond week 7. 86% of the women took statin treatment only during the first trimester and 6% continued into the second trimester. The median duration of statin treatment during pregnancy was 6 weeks. The frequency of major birth defects was non-significantly higher in the statin-exposed group (4.1% vs. 2.7%, OR=1.5, 95% CI 0.5-4.5, p=0.43). The frequency of miscarriage or fetal death was significantly higher in the statin-exposed group (14.5% vs. 7.6%, OR=2.1, 95% CI 1.1-3.8, p=0.016). The frequency of preterm delivery was significantly higher in the statin-exposed group (16.1% vs. 8.5%, OR=2.1, 95% CI 1.1-3.8, p=0.019). The median gestational age at birth was not significantly different between groups (39 vs. 39 weeks, p=0.27)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Median birthweight was similar between groups (3,280 vs. 3,250 g, p=0.95)
Taguchi et al. 2008 **Canada** **Prospective study**	NA	64 women with hypercholesterolemia who were pregnant or planning a pregnancy and taking a statin antenatally from 1998-2005. Women were recruited when they contacted the teratogen information service at a single hospital. Mean age was 33 years. Mean gestational age at recruitment was 6.5 weeks. Mean gravidity/parity was 2.4/1.1 64 pregnant women who had contacted the Motherisk program regarding therapeutic uses of non-teratogens. Mean age was 33 years. Mean gestational age was 7.1 weeks. Mean gravidity/parity was 2.3/1.0	Women were identified and followed for the duration of their pregnancy. Comparison of outcomes of statin exposed women vs. non-statin exposed. Pregnancy and neonatal outcomes were collected by telephone interview, using standardized questionnaires. Medical information was collected from treating physicians.	**Primary outcome:** Major birth defects **Secondary outcomes:** Pregnancy outcomes (lives births, still births, miscarriages, pregnancy terminations), gestational age and birth, birthweight and neonatal health problems.	The most commonly-used statin was atorvastatin (n=49). All but 3 women discontinued its use during the first trimester (mean 5.9 weeks). The time to discontinuation of the other statins was 8.3 weeks (n=9, simvastatin), 8.5 weeks (n=6, pravastatin) and 7.0 weeks (n=3, rosuvastatin). The number of birth defects was not significantly higher among the statin-exposed women (2.2% vs. 1.9%, p=0.93). The number of live births was similar between groups (71.9% vs. 81.2%, p=0.21). Mean gestational age at birth and birthweight were lower in the statin-exposed group (38.4 vs. 39.3, p=0.04 and 3.14 vs. 3.45 kg, p=0.01, respectively). There were 7 (15.2%) neonatal health problems in the statin-exposed group compared with 5 (9.6%) in the non-exposed group (p=0.40),
Ofori et al. 2007 **Canada** **Retrospective study**	NA	151 women, aged 15-45 years who had filled a prescription for a lipid-lowering drug (statin, fibrate, or nicotinic acid) drug in the year prior, or during their pregnancy, and which resulted in a live birth. Women were excluded if they had taken any other category	3 databases were linked to create a medication and pregnancy database, including data from all pregnancies that occurred in the province of Quebec from 1997-2003. 3 study groups were assembled and their outcomes compared with a control group, which	**Primary outcomes:** Minor and major congenital abnormalities within the first 12 months of birth	A link between mother and infant was established in: 64/69 cases (Group A); 14/15 (Group B) and 67/67 (Group C). The frequency of congenital abnormalities was: Group A 3/64; 4.69%, 95% CI 1.00-13.7% Group B 3/14; 21.43%, 95% CI 4.41-62.6% Group C 7/67, 10.45%; 95% CI 4.19-21.5% Controls 6.97%, 95% CI 6.8-7.17% Using Group B as the reference, and adjusting for

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		X medications.	consisted of the remaining cases in the assembled registry without congenital abnormalities. . Group A: women who filled a prescription for a statin before or during the first trimester (n=69); Group B: women who filled a prescription for a fibrate or nicotinic acid before or during the first trimester (n=15) and Group C: women who had filled a prescription for a statin in the period from one year before conception to one month before conception (n=67).		potential confounders, including maternal age at end of pregnancy, socioeconomic variables, and co-morbid conditions (diabetes, HTN etc.), the odds of a congenital abnormality were not increased significantly (Group A: OR=0.79, 95% CI 0.10-6.02 and Group C: OR=1.74, 95% CI 0.27-11.27).
Pollack et al. 2005 **USA** **Retrospective study**	NA	Reports collected up to 2002, of 477 women included in the Worldwide Adverse Experience System, Merk's postmaketing reporting surveillance, who were exposed to simvastatin and/or lovastatin during their pregnancy.	The pregnancy outcomes were classified as prospective (reports received after statin exposure, but prior to knowledge of pregnancy outcome) or retrospective (reports received after statin exposure and pregnancy outcome was known).	**Primary outcomes:** Congenital abnormalities, live births, elective abortions, spontaneous abortions, and fetal deaths	**Prospective reports** (n=386 cases): Mean maternal age, known in 291 cases, was 32 years. Cases were reported at an average of 10 weeks' gestation. Pregnancy outcomes were known for 225 cases. There were 6 reported congenital abnormalities (3.8%), which was similar to the US background rate of 3.15%. Among the cases of congenital abnormalities, 5 were live births and 1 was stillborn. All exposures to statins (simvastatin 10-20 mg/day) occurred during the first trimester. There were 49 elective abortions (21.7%), 18 spontaneous abortions (10.2%), 4 fetal deaths (2.5%) and 154 live births (68.4%). Of the 154 live births, statin exposures were reported in 150 cases. Statin therapy was discontinued in 122/135 cases, where gestational age was known. Statin therapy was initiated in the second trimester in 4 cases. **Retrospective reports** (n=91 cases): 13 congenital

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					abnormalities were reported in 8 live births. The timing of statin exposure was during the first trimester in 12/13 cases (timing of exposure was not known in 13th case). There were 5 cases of isolated abnormalities and 5 cases of multiple abnormalities.

Low-fat Diet to Reduce Serum Lipids during Pregnancy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Khoury et al. 2005 **Norway** **RCT** ***Cardiovascular Risk Reduction Diet in Pregnancy Trial (CARRDIP)***	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	29 non-smoking pregnant women aged 21-38 years with a BMI of 19-32, 17-20 weeks' gestation, who were not vegetarians, nor following a Mediterranean diet, were included. Women with high-risk pregnancies or those with medical complications were excluded. Mean age was 30years. Mean gestational age at study entry was 19 weeks.	Women were randomly allocated to the usual diet (n=149) or intervention diet (n=141) from study entry until delivery. The intervention diet aimed to limit dietary cholesterol to 150 mg/day and to reduce the intake of saturated fat to 8%, with 32% of total energy intake from fat. Energy intake aimed at a weight gain of 8 to 14 kg from pre-pregnancy levels. The consumption of fresh fruits, vegetables, low-fat dairy, lean meat and fish was encouraged. Women in the control group were encouraged to eat their usual diet. Compliance was assessed by the use of a 48-hr dietary recall. Fasting blood samples were obtained at baseline and weeks 24,30 and 36 gestation.	**Primary outcomes:** Total cholesterol (TC), HDL chol, LDL chol, triglycerides (TG) and Apolipoprotein B, fetal outcomes	There were 7 withdrawals from the control group and 14 from the intervention group. The mean daily intakes of calories, total fat, saturated fat and cholesterol were all significantly lower in the intervention group Mean TG levels increased over time in both groups, although they were significantly lower at weeks 24, 30 and 36 in the intervention group. Mean HDL chol levels decreased over the study period in both groups, although the decline was significantly greater in the intervention group. Mean LDL chol levels increased over the study period in both groups. The magnitude of the change was not as great for women in the intervention group (p=0.009). There were increases in mean TG and Apo B levels in both groups, but there were no significant differences between groups. There were significantly fewer preterm deliveries in the intervention group (7.4% vs. 0.7%, RR=0.10, 95% CI 0.01-0.77, p=0.006).

Diabetes

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Increased risk of Stroke Associated with Diabetes					
Scott et al. 2012 **UK** **Case-control study**	NA	A population-based database (Obstetric Surveillance System) including data from 229 hospitals collected from 2007-2010, was used to identify cases (pregnant women who had sustained an antenatal stroke, n=30) and controls (women who delivered immediately before the reported case, at the same hospital who had not sustained a stroke, n=89)	Risk factors for stroke were identified and used to develop a regression model, predictive of stroke	**Primary outcomes:** Stroke incidence and risk factors	During the study period, there were an estimated 1,958,203 deliveries. Among nonhemorrhagic strokes (n=18), there were 13 ischemic arterial strokes, 3 cases of cerebral venous thrombosis and 2 cases of carotid dissection. Among the hemorrhagic strokes (n=12), there were 9 ICHs and 3 SAHs. Overall stroke incidence was 1.5 cases/100,000 deliveries. Median gestational age at the time of stroke onset was 30 weeks. The odds of nonhemorrgahic stroke were increased for women with gestational diabetes (3 vs. 0, OR=21.1, 95% CI 2.2-∞). The odds of hemorrhagic stroke were increased for women with gestational diabetes (2 vs. 0, OR=19.3, 95% CI 1.5-∞). The adjusted odds of any stroke were increased for women with gestational diabetes (OR=26.8, 95% CI 3.2-∞).
James et al. 2005 **USA** **Retrospective study**	NA	2,850 women, included in the Nationwide Inpatient Sample from 2000-2001, who had been discharged from one of 1,000 hospitals with a pregnancy-related stroke diagnosis (707 hemorrhagic stroke, 766 ischemic stroke, 50 cerebral vein thrombosis and 1,327 pregnancy-related cerebrovascular events)	Medical records were reviewed. Non-adjusted models for pregnancy-related stroke risk and medical conditions and complications of pregnancy/delivery, were estimated.	Stroke risk	Overall, pregnancy-related stroke risk was 34.2 (95% CI 33.3-35.1)/ 100,000 pregnancies. The odds of stroke were significantly increased for women with diabetes (OR=2.5, 95% CI 1.3-4.6)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Increased Risk of Future Stroke Associated with Diabetes during Pregnancy					
Goueslard et al. 2016 **France** **Retrospective study**	NA	Women aged 14-51 years who had delivered in French hospitals from 2007-2008, who did and did not develop gestational diabetes (GDM). Women with pre-existing diabetes were excluded.	Using data from an administrative database, comparison of characteristics of women with and without gestational diabetes. Models were developed to identify independent predictors of cardiovascular diseases (CVD)	Incidence of CVD 7 years after delivery, including angina pectoris, MI, stroke, heart bypass, coronary angioplasty and endarterectomy and fibrinolysis intervention)	There were 62,958 cases of GDM and 1,452,429 without GDM. Women with GDM were significantly older than those without GDM, were more often obese, had a hypertensive disorder of pregnancy and went on to develop subsequent diabetes. GDM was an independent predictor of all CVD combined (OR=1.25, 95% CI 1.09-1.43), angina pectoris (OR=1.68, 95% CI 1.29-2.20), MI (OR=1.92, 95% CI 1.36-2.71) and hypertensive diseases (OR=2.72, 95% CI 2.58-2.88), after adjusting for age, obesity, subsequent diabetes and hypertensive disease during pregnancy. While more women with GDM experienced an ischemic stroke (0.11% vs. 0.09%, p<0.05), GMD was not an independent predictor.
Archambault et al. 2014 **Canada** **Scoping review**	NA	6 studies that included stratified samples of pregnant women with and without gestational diabetes and reported a cardiovascular outcome	Narrative synthesis of results	Cardiovascular disease	Median duration of follow-up ranged from 3.6-12.5 years A single study reported stroke as a cardiovascular end point. Gestational diabetes was not associated with increased odds of stroke, adjusting for age and menopausal status (OR=1.67, 95% CI 0.87-3.22)
Savitz et al. 2014 **USA** **Retrospective study**	NA	Birth certificate for 849,639 live births in New York City from 1995-2004 were linked to hospital discharge data. Women with pre-existing cardiovascular disease, hypertension, or diabetes prior to delivery, and multiple births were excluded.	The relationship between cardiovascular diseases that occurred within the first year following delivery and gestational diabetes (and other pregnancy complications) was examined. Outcome data was obtained from discharge records.	Heart failure, stroke/TIA, ICH Models were adjusted for age, race, health insurance, gestational HTN, preeclampsia, parity, education, smoking, prenatal care and pre-pregnancy weight	There were 14.8 strokes/TIA and 8.0 ICH/100,000 live births during the 1-year follow-up The odds of stroke/TIA or ICH, given the presence of gestational diabetes, were not significantly increased (OR=1.2, 95% CI 0.7-2.3 and OR=1.5, 95% CI 0.7-3.4, respectively). The odds of developing type I and type 2 diabetes were increased significantly (OR=40.4, 95% CI 23.8-68.5 and OR=22.6, 95% CI 16.9-30.4, respectively)
Shah et al. 2008 **Canada** **Case-control**	NA	Women with and without gestational diabetes (GDM), aged 20-49 years who had delivered in an Ontario hospital from	Patients were followed until 2007, at which point the incidence of the primary outcome was compared between cases	CVD events (hospitalizations for MI, stroke, CABG, coronary angioplasty, or carotid endarterectomy	8,191 were identified with GDM and 81,262 without GDM. Median duration of follow-up was 11.5 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
study		1994-1997. Mean age was 31 years.	and controls (matched 10:1 per case).		The risk of overall CVD was significantly higher for women with GDM (HR=1.71, 95% CI 1.08-2.69), but when the analysis was adjusted for subsequent diabetes, the risk was no longer significantly elevated (HR=1.13, 95% CI 0.67-1.89).
Dietary Interventions for Women with Gestational Diabetes					
Ma et al. 2014 **China** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	95 women aged 18-40 years, with gestational diabetes, at 24-26 weeks' gestation. Women with pre-existing DM, multiple gestations and those with other serious diseases were excluded. Mean age was 30 years. Mean gestational age at study entry was 56.7 weeks.	Women were randomized to a control group (n=48) or a low glycemic load (GL) group (n=47). Women in both groups received individualized general dietary instruction every two weeks until delivery. Women in the control group were encouraged to select starches that were intermediate-high GL, while women in the intervention groups were encouraged to select foods with a low GL. Compliance was assessed every two weeks using a 3-day food recall. Blood samples were obtained pre- and post-intervention	Fasting plasma glucose (FPG), HgA1c and 2-hour post-prandial glucose (PPG), serum lipid	The mean daily glycemic load decreased among women in both groups, but significantly more so for women in the intervention group (-62.6 vs. -67.4, p<0.01). The mean FPG decreased among women in both groups, but significantly more so for women in the intervention group (-0.05 vs. -0.33, p<0.01). The mean 2h PPG decreased among women in both groups, but significantly more so for women in the intervention group (-2.51 vs. -2.98, p=0.003). There were no significant changes in mean HgA1C in women in either group. Mean total cholesterol and triglycerides increased in women in both groups, although the increases were not as great among women in the intervention group. Similarly, HDL chol decreased in women in both groups, although the mean decrease was not as great among women in the intervention group.
Asemi et al. 2013 **Iran** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☒	40 women aged 18-40 years with gestational diabetes mellitus, 24-28 weeks' gestation, were included. Women with a previous history of DM, smokers, and those with kidney or liver disease were excluded as were women with hypothyroidism. Mean maternal age was 29.5 years.	Women were randomly assigned (1) to the control or the DASH diet for 4 weeks. They were asked not to alter their routine physical activity and did not receive any lipid-lowering medications. The control diet was designed to contain 45–55 % carbohydrates, 15–20 % protein and 25–30 % total	Fasting plasma glucose, glucose tolerance tests (1,2 and 3 hours), HgA1C, Total cholesterol (TC), HDL chol, LDL chol, TC: HDL chol, Systolic blood pressure (SBP), diastolic blood pressure (DBP)	3 women in each group were lost to follow-up. There were no differences from pre- to post intervention between groups in weight or BMI. The mean daily intakes of total fat, saturated fat, dietary cholesterol, dietary fibre, sucrose and sodium were significantly lower in the DASH group, while DASH group women consumed significantly more daily servings of fruit, vegetables and nuts, while consuming fewer servings of fats and oils. Despite improvements in some markers in both groups

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			fat, and was similar in macronutrient composition to the DASH diet. The DASH diet was rich in fruits, vegetables, whole grains, low-fat dairy products, and was low in saturated fats, cholesterol, refined grains, sweets and sodium (2400 mg/d). 3-day food records were used to examine nutrient intakes.		and over time (eg., mean change of -0.45 mmol/L 1-hour GGT in control group vs. a mean change of -1.86 mmol/L in DASH group, p><0.0001 for time, p=0.05 for group), there were no significant differences between groups (group x time interaction) for any of the outcomes

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