

**Evidence evaluation report —
Detecting undiagnosed diabetes in early pregnancy**

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PROCESS OF THE REVIEW

Research questions

1. What is the most appropriate screening test to detect undiagnosed diabetes in early pregnancy?
2. To whom should it be applied?
3. What are the additional considerations for Aboriginal and Torres Strait Islander women?
4. What are additional considerations for women from culturally and linguistically diverse backgrounds?

Search strategy

Databases searched:

- EMBASE (OVID) AND MEDLINE (OVID) and PSYCHINFO (OVID) = 210
- COCHRANE LIBRARY = 13
- CINAHL = 30
- AUSTRALIAN INDIGENOUS HEALTHINFONET = 17

Date of searches: 15/06/2016

Dates searched: 2008 to present

Full search strategies

EMBASE AND MEDLINE AND PSYCHINFO (OVID)

1. ((undiagnosed or undetected or pre-existing or (type 1) or (type I) or (type 2) or (type II)) adj diabetes).tw.
2. ((early pregnancy) or (first trimester) or booking or (first antenatal)).tw.
3. (screen* or test* or diagnos* or detect*).tw.
4. 1 and 2 and 3
5. 2008 to current

COCHRANE

1. ((undiagnosed or undetected or pre-existing or "type 1" or "type I" or "type 2" or "type II") next diabetes):ti,ab,kw
2. ("early pregnancy" or "first trimester" or booking or "first antenatal"):ti,ab,kw
3. (screen* or test* or diagnos* or detect*):ti,ab,kw
4. #1 and #2 and #3
5. 2008 to current

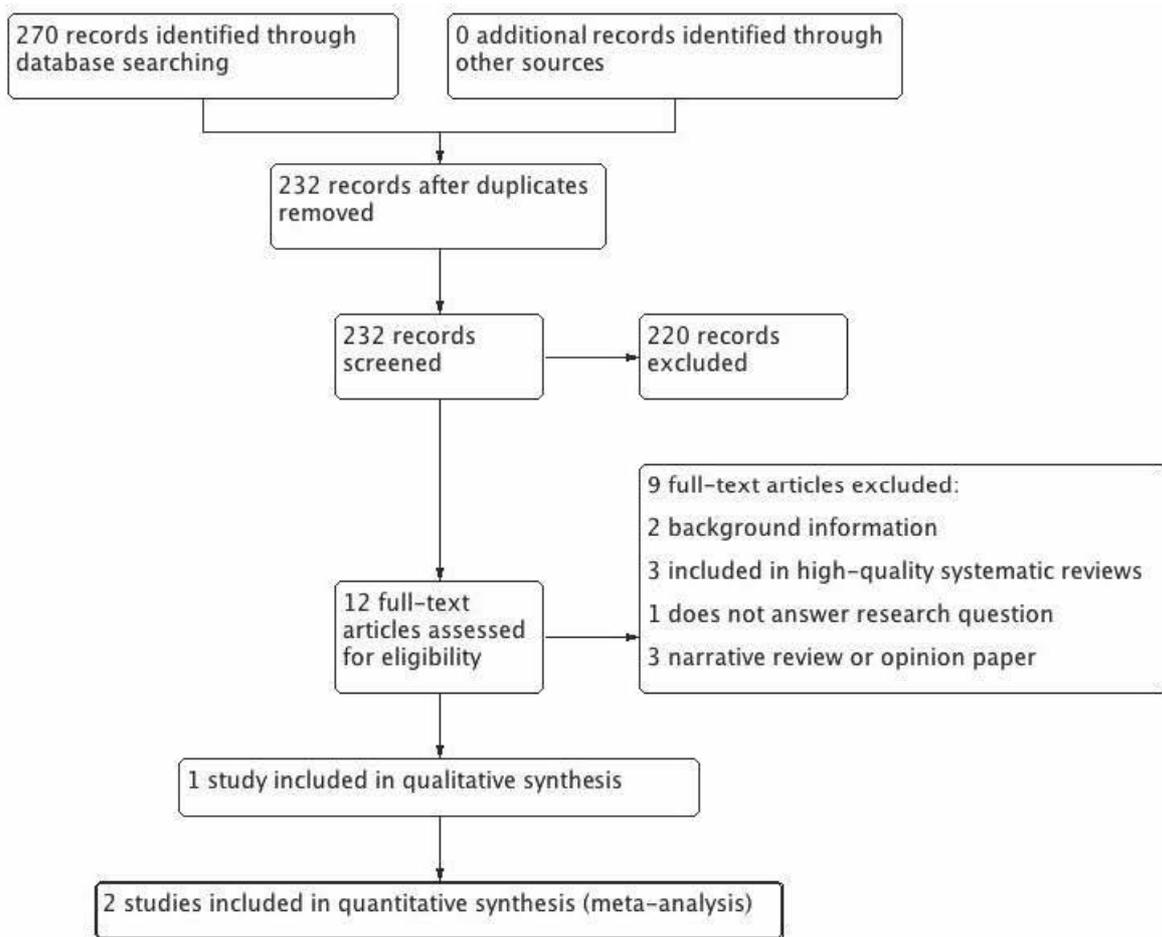
CINAHL

1. ((undiagnosed or undetected or pre-existing or "type 1" or "type I" or "type 2" or "type II") N1 diabetes)
2. ("early pregnancy" or "first trimester" or booking or "first antenatal")
3. (screen* or test* or diagnos* or detect*)
4. S1 and S2 and S2
5. 2008 to current

AUSTRALIAN INDIGENOUS HEALTHINFONET

Title: diabetes AND pregnan*

2008 to current



Prisma flow diagram

Exclusion criteria

Full texts of 12 papers identified as within the review period and in English were reviewed. Exclusion criteria included:

- background information
- already included in high quality systematic reviews
- not specific to target population (eg specific to non-pregnant women or high-risk women only)
- does not answer research question
- narrative review or opinion paper (editorial, letter, comment).

The three remaining studies (one of which was a good quality systematic review) were included in the appraisal of the evidence.

Assigning level of evidence

Levels of evidence were assigned using the NHMRC levels (screening intervention for all research questions) and the definitions given below.

Designations of levels of evidence

Level	Screening intervention
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	Pseudo-randomised controlled trial (ie alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none">▪ Non-randomised, experimental trial▪ Cohort study▪ Case-control study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none">▪ Historical control study▪ Two or more single arm study
IV	Case series

Source: NHMRC (2009) *NHMRC levels of evidence and grades of recommendations for developers of guidelines*.

Study design definitions

- **A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation** — a cross-sectional study where a consecutive group of people from an appropriate (relevant) population receive the test under study (index test) and the reference standard test. The index test result is not incorporated in (is independent of) the reference test result/final diagnosis. The assessor determining the results of the index test is blinded to the results of the reference standard test and vice versa.
- **A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation** — a cross-sectional study where a non-consecutive group of people from an appropriate (relevant) population receive the test under study (index test) and the reference standard test. The index test result is not incorporated in (is independent of) the reference test result/final diagnosis. The assessor determining the results of the index test is blinded to the results of the reference standard test and vice versa.
- **Case series** — a single group of people exposed to the intervention (factor under study). **Post-test** – only outcomes after the intervention (factor under study) are recorded in the series of people, so no comparisons can be made. **Pre-test/post-test** – measures on an outcome are taken before and after the intervention is introduced to a series of people and are then compared (also known as a 'before- and-after study').
- **Case-control study** — people with the outcome or disease (cases) and an appropriate group of controls without the outcome or disease (controls) are selected and information obtained about their previous exposure/non-exposure to the intervention or factor under study.
- **Diagnostic (test) accuracy** – in diagnostic accuracy studies, the outcomes from one or more diagnostic tests under evaluation (the *index test/s*) are compared with outcomes from a *reference standard test*. These outcomes are measured in individuals who are suspected of having the condition of interest. The term *accuracy* refers to the amount of agreement between the index test and the reference standard test in terms of outcome measurement. Diagnostic accuracy can be expressed in many ways, including sensitivity and specificity, likelihood ratios, diagnostic odds ratio, and the area under a receiver operator characteristic (ROC) curve.

- **Diagnostic case-control study** – the index test results for a group of patients already known to have the disease (through the reference standard) are compared to the index test results with a separate group of normal/healthy people known to be free of the disease (through the use of the reference standard). In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice. *Note: this does not apply to well-designed population based case-control studies.*
- **Historical control study** – outcomes for a prospectively collected group of people exposed to the intervention (factor under study) are compared with either (1) the outcomes of people treated at the same institution prior to the introduction of the intervention (ie. control group/usual care), or (2) the outcomes of a previously published series of people undergoing the alternate or control intervention.
- **Non-randomised, experimental trial** - the unit of experimentation (eg. people, a cluster of people) is allocated to either an intervention group or a control group, using a non-random method (such as patient or clinician preference/availability) and the outcomes from each group are compared. This can include:
 - **a controlled before-and-after study**, where outcome measurements are taken before and after the intervention is introduced, and compared at the same time point to outcome measures in the (control) group.
 - **an adjusted indirect comparison**, where two randomised controlled trials compare different interventions to the same comparator ie. the placebo or control condition. The outcomes from the two interventions are then compared indirectly.
- **Prospective cohort study** — where groups of people (cohorts) are observed at a point in time to be exposed or not exposed to an intervention (or the factor under study) and then are followed prospectively with further outcomes recorded as they happen.
- **Pseudo-randomised controlled trial** - the unit of experimentation (eg. people, a cluster of people) is allocated to either an intervention (the factor under study) group or a control group, using a pseudo-random method (such as alternate allocation, allocation by days of the week or odd-even study numbers) and the outcomes from each group are compared.
- **Randomised controlled trial** — the unit of experimentation (eg. people, or a cluster of people⁴) is allocated to either an intervention (the factor under study) group or a control group, using a random mechanism (such as a coin toss, random number table, computer-generated random numbers) and the outcomes from each group are compared.
- **Retrospective cohort study** — where the cohorts (groups of people exposed and not exposed) are defined at a point of time in the past and information collected on subsequent outcomes, eg. the use of medical records to identify a group of women using oral contraceptives five years ago, and a group of women not using oral contraceptives, and then contacting these women or identifying in subsequent medical records the development of deep vein thrombosis.
- **Study of diagnostic yield** — these studies provide the yield of diagnosed patients, as determined by the index test, without confirmation of the accuracy of the diagnosis (ie. whether the patient is actually diseased) by a reference standard test.
- **Systematic literature review** — systematic location, appraisal and synthesis of evidence from scientific studies.
- **Two or more single arm study** – the outcomes of a single series of people receiving an intervention (case series) from two or more studies are compared.

Source: NHMRC (2009) *NHMRC levels of evidence and grades of recommendations for developers of guidelines.*

Selection of outcomes for GRADE analysis

Outcomes considered for inclusion comprised conditions known to be associated with diabetes in pregnancy. Seven outcomes were selected on the basis of clinical impact.

Outcome	Importance	Inclusion
Perinatal death	9	<input checked="" type="checkbox"/>
Major congenital anomalies	9	<input checked="" type="checkbox"/>
Preterm birth <37 weeks	9	<input checked="" type="checkbox"/>
Pre-eclampsia	9	<input checked="" type="checkbox"/>
Induced labour	8	<input checked="" type="checkbox"/>
Large for gestational age (>90 th percentile)	9	<input checked="" type="checkbox"/>
Macrosomia (birth weight >4,000 g)	9	<input checked="" type="checkbox"/>

Key: 1 – 3 less important; 4 – 6 important but not critical for making a decision; 7 – 9 critical for making a decision

Evidence tables

1. What is the most appropriate screening test to detect undiagnosed diabetes in early pregnancy?

Evidence summary

The identified evidence for question 1 was limited and largely comprises the relevant findings of the systematic literature review conducted to inform the development of the 2014 New Zealand guidelines on screening, diagnosis and management of gestational diabetes (NZ MoH 2014).

Screening test

The research question in the New Zealand guidelines was specific to screening using glycated haemoglobin (HbA1c) before 20 weeks gestation.

No additional studies were identified that investigated detection of undiagnosed diabetes using other screening tests in early pregnancy or that reported on the sensitivity and specificity of HbA1c against a reference test.

Screening threshold

A New Zealand prospective cohort study (included in the systematic review) (Hughes et al 2014) reported on the use of HbA1c for detecting diabetes in early pregnancy and examined outcomes associated with different thresholds (using thresholds similar to those recommended by the American Diabetes Association for detecting prediabetes in non-pregnant people ie 41.4–46.7 mmol/mol (ADA 2015)). Among women who also undertook oral glucose tolerance testing (OGTT) at <20 wk (23%), HbA1c \geq 41 mmol/mol identified all 15 cases of diabetes and had sensitivity of 100% (95%CI 91.8 to 100) and specificity of 97.4% (95%CI 95.5 to 99.2). Women with HbA1c of 41–46 mmol/mol (n=200) had poorer pregnancy outcomes than those with HbA1c <41 mmol/mol (n=7,897) (low quality).

Harms and benefits of screening

The New Zealand guidelines found that, although the addition of an HbA1c blood test at the first antenatal visit is unlikely to inconvenience women, insufficient research was identified to adequately assess the balance of benefits and harms for either all pregnant women or those with risk factors.

An additional prospective cohort study found that, although smaller numbers in the higher risk groups limited the power to see significant differences in outcomes, earlier treatment (<24 weeks) based on an HbA1c of 41–49 mmol/mol was associated with a reduced risk of pre-eclampsia compared with treatment \geq 24 weeks (1.5 vs 8.0%, adjusted P=0.03) (Rowan et al 2016). There was no statistical difference found for other pregnancy (gestational hypertension, induced labour, Caesarean section) or neonatal (gestational age at birth, birth weight, admission to neonatal intensive care, mortality) outcomes between groups.

Uptake of early screening

A New Zealand study (Hughes et al 2016b) compared uptake of first antenatal bloods with that of screening for gestational diabetes (glucose challenge tests, OGTT) to assess changes in uptake of screening for diabetes if HbA1c was added to first antenatal bloods. It found that universal early pregnancy HbA1c measurement would particularly benefit populations with both high rates of unrecognised type 2 diabetes and a low uptake of gestational diabetes screening in later pregnancy.

New Zealand recommendations

The NZ guidelines recommend offering HbA1c to all women at the first antenatal visit (*qualified recommendation*) and for women with:

- HbA1c \geq 50 mmol/mol, care provided by a service that specialises in diabetes in pregnancy (*qualified recommendation*)
- HbA1c 41–49 mmol/mol, dietary and lifestyle advice and oral glucose tolerance testing at 24–28 weeks (*good practice point*).

It recommends against use of HbA1c as a test for **gestational diabetes** due to a lack of sensitivity (*qualified recommendation*).

Additional information

The International Association of Diabetes Study Groups (IADSPG) (Metzger et al 2010) recommends a threshold of ≥ 47.5 mmol/mol if HbA1c is used to detect pre-existing diabetes in pregnancy.

Advice to EWG

The evidence on whether HbA1c may be an appropriate screening test to detect undiagnosed diabetes in early pregnancy is limited. While the harms and benefits of its use have not been sufficiently evaluated, it has the potential to increase uptake of screening and to identify women at increased risk of poorer pregnancy outcomes associated with hyperglycaemia. Further research (ie RCTs) is needed to evaluate the benefit of early treatment for hyperglycaemia in pregnancy.

Note that the Medicare Benefits Schedule does not include HbA1c as a diagnostic test in pregnancy.

Evidence statements

Outcomes associated with HbA1c 41–46 mmol/mol compared to HbA1c <41 mmol/mol in early pregnancy

- Compared to women with HbA1c <41 mmol/mol in early pregnancy, women with HbA1c 41–46 mmol/mol had a higher risk of perinatal death, major congenital anomalies, preterm birth, pre-eclampsia, induced labour and large for gestational baby and the difference in rates of macrosomia did not reach significance (low quality evidence).

Outcomes associated with early treatment compared to later treatment for women with HbA1c 41–49 mmol/mol

- Treatment before 24 weeks was associated with a lower risk of pre-eclampsia than treatment at or after 24 weeks but the differences in other outcomes (perinatal death, preterm birth, induced labour, large for gestation age and macrosomia) did not reach significance (low quality evidence).

Summary of findings

Pregnancy outcomes associated with HbA1c 41–46 mmol/mol compared to HbA1c <41 mmol/mol in early pregnancy

Patient or population: Pregnant women ≤ 20 weeks gestation (excluding those referred for management of gestational diabetes)

Setting: New Zealand

Testing threshold: HbA1c 41–46 mmol/mol

Comparison: HbA1c <41 mmol/mol

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with HbA1c <41 mmol/mol	Risk with HbA1c 41–46 mmol/mol				
Perinatal death	5 per 1,000	19 per 1,000 (7 to 48)	RR 3.96 (1.54 to 10.16)	8,187 (1 observational study)	 LOW ¹	
Major congenital anomalies	13 per 1,000	34 per 1,000 (17 to 71)	RR 2.67 (1.28 to 5.53)	8,187 (1 observational study)	 LOW ¹	
Preterm birth <37 wk	49 per 1,000	81 per 1,000 (50 to 134)	RR 1.66 (1.01 to 2.74)	8,187 (1 observational study)	 LOW ¹	
Pre-eclampsia	23 per 1,000	55 per 1,000 (30 to 99)	RR 2.42 (1.34 to 4.38)	8,187 (1 observational study)	 LOW ¹	
Induced labour	127 per 1,000	183 per 1,000 (128 to 262)	RR 1.44 (1.01 to 2.06)	8,187 (1 observational study)	 LOW ¹	

Pregnancy outcomes associated with HbA1c 41–46 mmol/mol compared to HbA1c <41 mmol/mol in early pregnancy

Patient or population: Pregnant women ≤20 weeks gestation (excluding those referred for management of gestational diabetes)

Setting: New Zealand

Testing threshold: HbA1c 41–46 mmol/mol

Comparison: HbA1c <41 mmol/mol

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with HbA1c <41 mmol/mol	Risk with HbA1c 41–46 mmol/mol				
Large for gestational age (>90 th percentile)	82 per 1,000	136 per 1,000 (91 to 203)	RR 1.66 (1.11 to 2.48)	8,186 (1 observational study)	⊕⊕○○ LOW ¹	
Macrosomia (>4,000g)	155 per 1,000	174 per 1,000 (121 to 250)	RR 1.12 (0.78 to 1.61)	8,186 (1 observational study)	⊕⊕○○ LOW ¹	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Source: Hughes et al 2014. Note that this study was included in MoH NZ 2014 but is presented separately here to inform the analysis.

1. Data from a single observational study with low rates of participation in reference testing

Pregnancy outcomes associated with early treatment compared to later treatment for women with HbA1c 41–49 mmol/mol

Patient or population: Pregnant women

Setting: New Zealand

Intervention: Early treatment (<24 weeks)

Comparison: Later treatment (≥24 weeks)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with later treatment (≥24 wk)	Risk with early treatment (<24 wk)				
Perinatal death	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	285 (1 observational study)	⊕⊕○○ LOW ¹	
Major congenital anomalies	Not reported					
Preterm birth <37 weeks	166 per 1,000	104 per 1,000 (56 to 192)	RR 0.63 (0.34 to 1.16)	285 (1 observational study)	⊕⊕○○ LOW ¹	
Pre-eclampsia	79 per 1,000	15 per 1,000 (3 to 65)	RR 0.19 (0.04 to 0.82)	285 (1 observational study)	⊕⊕○○ LOW ¹	
Induced labour	589 per 1,000	607 per 1,000 (501 to 731)	RR 1.03 (0.85 to 1.24)	285 (1 observational study)	⊕⊕○○ LOW ¹	
Large for gestational age (>90th percentile)	106 per 1,000	90 per 1,000 (43 to 182)	RR 0.85 (0.41 to 1.72)	285 (1 observational study)	⊕⊕○○ LOW ¹	
Macrosomia (>4,000g)	86 per 1,000	43 per 1,000 (15 to 116)	RR 0.50 (0.18 to 1.35)	285 (1 observational study)	⊕⊕○○ LOW ¹	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Source: Rowan et al 2016.

1. Data from a single small observational study.

1.1 Test

Study ref	Design	LoE	N	Questions and findings	Individual studies	Comments
(NZ MoH 2014)	SLR	I	3 studies	<p>Question: The systematic review conducted to inform the guidelines asked the clinical question: <i>Should all pregnant women less than 20 weeks gestation be offered an HbA1c test to test for type 2 diabetes?</i></p> <p>Studies: The review identified three observational studies that assessed HbA1c as an early test in pregnant women.</p> <p>Summary: There is minimal evidence to determine if all pregnant women at less than 20 weeks' gestation should be offered an HbA1c to detect previously undiagnosed type 2 diabetes. Recommendations from guidelines and position statements for HbA1c testing of all women or women with risk factors prior to 20 weeks appear to have been mostly derived from extrapolation from non-pregnant populations.</p>	<p>One study (n=296) tested using HbA1c test at the first antenatal visit (all prior to 20 weeks) (Moore & Clokey 2013). Women with an HbA1c ≥ 48 mmol/mol (group 1) were considered to have diabetes and were instructed on diet and daily self-monitoring of blood glucose. Those with an HbA1c between 39 and 47 mmol/mol (group 2) were considered to have glucose intolerance and were tested immediately for gestational diabetes and if necessary again at 24–28 weeks. Women with an HbA1c < 39 mmol/mol (group 3) were tested at 24–28 weeks for gestational diabetes.</p> <p>The authors concluded that HbA1c testing at the first antenatal visit can be used to optimise the timing of later testing for gestational diabetes. The study did not have a control group so it was unable to determine whether testing early in pregnancy was associated with beneficial outcomes for pregnant women.</p>	

Study ref	Design	LoE	N	Questions and findings	Individual studies	Comments
					<p>A Japanese study assessed four different approaches to detecting gestational diabetes (50 g oral glucose challenge test, random plasma glucose (RPG) measurement, HbA1c and fasting blood glucose) and compared testing in the first and second trimesters of pregnancy (Maegawa et al 2003). Gestational diabetes was confirmed with a 75 g oral glucose tolerance test within four weeks of being tested. The glucose challenge test was found to be the optimal test for gestational diabetes testing based on assessments of different thresholds of the tests used. The authors conclude that first trimester testing for glucose intolerance was important as it suggests that the problem was probably present before pregnancy.</p>	

Study ref	Design	LoE	N	Questions and findings	Individual studies	Comments
					<p>In the New Zealand STEP study, women (n=16,122) were tested with an HbA1c and random blood glucose (RBG) measured with the first antenatal blood tests (Hughes et al 2014). Women with HbA1c \geq 38 mmol/mol or a RBG \geq 5.5 mmol/L and a consecutive series of 1,000 women with results below these thresholds (control group) were invited to have a 2-hour, 75 g OGTT before 20 weeks' gestation. Diabetes in pregnancy and gestational diabetes were diagnosed by WHO glucose criteria. The uptake of the diagnostic invitation (OGTT) was very low: 16.4% of the control group and 21.3% of those women above the threshold participated. An early OGTT was performed for only 983 women; however, the analysis weighted the results to adjust for the discrepancy in the number of women with low and high test results.</p> <p>The authors conclude that the HbA1c test was superior to RBG for detecting probable undiagnosed diabetes in pregnancy (RBG data not reported). The authors note the need for studies confirming that earlier treatment improves pregnancy outcomes.</p>	

1.2 Test threshold

Study ref	Design	LoE	N	Questions and findings	Individual studies	Comments
(NZ MoH 2014)	SLR	I	2 studies	<p>Question: <i>What thresholds should be used to identify type 2 diabetes in pregnant women less than 20 weeks gestation?</i></p> <p>Studies: Two studies with direct evidence from women early in pregnancy were identified.</p> <p>Summary: One primary study had insufficient numbers to adequately assess thresholds in pregnant women. However, a recent New Zealand study has reported high sensitivity 100% (95% CI 91.8–100) and specificity 97.4% (95% CI 95.5–99.2) using an HbA1c threshold of ≥ 41 mmol/mol for detecting probable undiagnosed diabetes in pregnancy.</p>	<p>In a retrospective cohort of women diagnosed with gestational diabetes (Burlingame et al 2012), women had an antepartum HbA1c test (at different gestational weeks) and a postpartum 75 g OGTT to diagnose probable undiagnosed type 2 diabetes. Almost 8% of 403 women who had an HbA1c test result ≥ 48 mmol/mol were diagnosed with diabetes postpartum.</p> <p>The authors were unable to demonstrate a clinically useful positive predictive value for defining type 2 diabetes using the HbA1c threshold of ≥ 48 mmol/mol. Numbers of participants were limited and 87% had their HbA1c test after 20 weeks.</p>	

Study ref	Design	LoE	N	Questions and findings	Individual studies	Comments
					<p>In the STEP study (Hughes & Moore 2013; Hughes et al 2014), the optimal threshold for diabetes was ≥ 41 mmol/mol (sensitivity 100% [9%CI 91.8 to 100%], specificity 97.4% (95%CI 95.5 to 99.2%]). In this population (which had a low prevalence for diabetes) the positive predictive value was 18.8% (95%CI 15.7 to 22.4). No RBG threshold had an adequate sensitivity and specificity combination for testing purposes.</p> <p>HbA1c ≥ 41 mmol/mol was seen in 2.9% of the women tested.</p> <p>In the total cohort, excluding women referred for management of diabetes, women with HbA1c of 41–46 mmol/mol (n=200) had poorer pregnancy outcomes than those with HbA1c <41 mmol/mol (n=8,174): relative risk (95%CI) of major congenital anomaly was 2.67 (1.28–5.53), pre-eclampsia was 2.42 (1.34–4.38), shoulder dystocia was 2.47 (1.05–5.85), and perinatal death was 3.96 (1.54–10.16).</p> <p>A threshold of ≥ 41 mmol/mol was also highly specific (98.4%; 95%CI 97.0 to 99.9%) but less sensitive (18.8%; 95%CI 6.6 to 31.1%) for gestational diabetes before 20 weeks (positive predictive value 52.9%) and in total 74% of women with an HbA1c above this threshold developed gestational diabetes (using WHO/IADPSG criteria) at some stage in pregnancy.</p> <p>Women with an HbA1c value <41 mmol/mol require further testing for gestational diabetes in later pregnancy (24–28 weeks' gestation).</p>	

1.3 Harms and benefits of testing

Study ref	Design	LoE	N	Aim, setting, population, measurements	Results	Comments
(Rowan et al 2016)	Cohort	III-2	946	<p>Aim: To examine whether women with an HbA1c of 41–49 mmol/mol (5.9–6.6%) are at higher risk than women with an HbA1c of <41 mmol/mol (5.9%) and whether pregnancy outcomes are improved if treated at <24 weeks' gestation.</p> <p>Setting: New Zealand</p> <p>Population: Women with diabetes in pregnancy diagnosed by early HbA1c testing or subsequent OGTT at <34 weeks' gestation</p> <p>Methods: Data were extracted from the hospital database. Women with HbA1c 41–49 mmol/mol (5.9–6.6%) were divided into those seen <24 weeks (Early, n=134) and those seen ≥ 24 weeks (Later, n=151). Those with HbA1c < 41 mmol/mol (5.9%) were labelled Other GDM (n=661).</p>	<p>There were higher rates of adverse outcomes in the Later group than the Other GDM group (pre-eclampsia 8.0 vs 2.4%, P=0.001, preterm birth 16.6 vs 8.2%, P=0.002, neonatal admission 15.5 vs 9.2%, P=0.02).</p> <p>Outcomes were similar between the Early group and Other GDM group (pre-eclampsia 1.5 vs 2.4%, P=0.5, preterm birth 10.5 vs 8.2% P=0.4, neonatal admission 13.6 vs 9.2%, P=0.12).</p> <p>Comparing the Early and Later groups, the Early group had less pre-eclampsia, 1.5 vs 8.0%, adjusted P=0.03. Other outcomes were not statistically different.</p>	

1.4 Uptake of HbA1c compared to glucose challenge test and oral glucose tolerance test

Study ref	Design	LoE	N	Aim, setting, population, measurements	Results	Comments
(Hughes et al 2016b)	Cohort	III-2	11,580	<p>Aim: to compare inter-ethnic antenatal testing practices to examine whether the HbA1c test would be accessed by ethnicities most at risk of diabetes and to determine the prevalence of unrecognised type 2 diabetes and prediabetes in our pregnant population.</p> <p>Setting: Christchurch, New Zealand</p> <p>Population: Pregnant women attending for antenatal care.</p> <p>Methods: Utilising electronic databases, we matched maternal characteristics to first-antenatal bloods, HbA1c, and GDM tests (glucose challenge tests and oral glucose tolerance tests).</p>	Overall uptake of the first-antenatal bloods versus GDM testing was 83.1% and 53.8% respectively in 11,580 pregnancies. GDM screening was lowest in Maori 39.3%, incidence proportion ratio (IPR) 0.77 (0.71, 0.84) compared with Europeans. By including HbA1c with the first-antenatal bloods, the number tested for diabetes increases by 28.5% in Europeans, 40.0% in Maori, 28.1% in Pacific People, and 26.7% in 'Others' (majority of Asian descent).	

1.5 Excluded studies for research question 1

Background information for research question 1

Study

(Sweeting et al 2016)	Despite early testing and current best practice treatment, early gestational diabetes in high-risk women remains associated with poorer pregnancy outcomes. Outcomes for those in whom diabetes was diagnosed at <12 weeks of gestation approximated those seen in pre-existing diabetes. These findings indicate the need for further studies to establish the efficacy of alternative management approaches to improve outcomes in these high-risk pregnancies.
(Hughes et al 2016a)	Physiological changes lower HbA1c levels, and pregnancy-specific reference ranges may need to be recognised. Other factors that influence HbA1c are also important to consider, particularly since emerging data suggest that, in early pregnancy, HbA1c elevations close to the reference range may both identify women with underlying hyperglycaemia and be associated with adverse pregnancy outcomes. In later pregnancy, HbA1c analysis is less useful than OGTT in detecting gestational diabetes.

Studies included in high-quality systematic reviews included in this review

Study

Moore, L. & Clokey, D. (2013) 275: A1C at the first prenatal visit: is it useful?" American Journal of Obstetrics & Gynecology 208(1): S125. (Conference abstract)

Hughes RC, Moore MP, Gullam JE et al (2014) An early pregnancy HbA1c \geq 5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. *Diabetes Care* 37: 2953–59.

Chamberlain C, McNamara B, Williams ED et al (2013) Diabetes in pregnancy among indigenous women in Australia, Canada, New Zealand and the United States. *Diabetes Metab Res Rev* 29(4): 241-56.

Other excluded studies

Study

Reason for exclusion

Allnutt Katherine, J., A. Allan Carolyn, et al. (2015) Early pregnancy screening for identification of undiagnosed pre-existing diabetes to improve maternal and infant health. DOI: 10.1002/14651858.CD011601

Review protocol

Anderson, H. B., S. Rezai, et al. (2015). "Comment on Hughes et al. An early pregnancy HbA1c \geq 5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. *Diabetes Care* 2014;37:2953–2959." *Diabetes Care* 38(6): e92.

Letter

Hughes, R. C., M. P. Moore, et al. (2015). "Response to comment on Hughes et al. An early pregnancy HbA1c \geq 5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. *Diabetes Care* 2014;37:2953–2959." *Diabetes Care* 38(6): e93.

Letter

Wong T, Ross GP, Jalaludin BB et al (2013) The clinical significance of overt diabetes in pregnancy. *Diabet Med* 30(4): 468-74.

Does not answer research question (not specific to early pregnancy)

2 To whom should it be applied?

Evidence summary

Testing versus no testing

The New Zealand Guideline Development Team noted that questions regarding testing versus no testing are only definitively answered by randomised controlled trials that compare morbidity and/or mortality outcomes among groups randomised either to testing or no testing. No randomised controlled trials have been performed and are unlikely to take place in the future. Current evidence consists of consensus statements and observational studies.

Universal testing versus case finding

The New Zealand Guideline Development Team took into consideration the high prevalence of previously undiagnosed diabetes and gestational diabetes in certain areas of New Zealand and the high chance that many women would have one or more risk factors (NZ MoH 2014). It decided that using universal testing at booking would be more appropriate in the New Zealand context than risk-based testing in early pregnancy.

Groups at risk

The New Zealand systematic review (NZ MoH 2014) identified 6 systematic reviews and 58 additional observational studies investigating risk factors for diabetes in pregnancy. Overall the quality of the evidence was very low due to the study design used and variability in the confounding variables included in the statistical analysis where reported. It is likely that interactions between risk factors, rather than any single risk factor, predispose a woman to gestational diabetes.

See also research questions 3 and 4.

Background information

Among women who gave birth in Australia in 2013, rates of pre-existing diabetes were (AIHW 2016):

- lowest among women aged <20 years (0.4%) and highest among women aged ≥40 years
- lower among nulliparous women (1.0%) than among women of higher parity (ie 1.9% for parity of four)
- higher among Aboriginal and Torres Strait Islander women (4.4%) than among non-Indigenous women (1.1%) (age-standardised)
- higher among women born overseas (1.2%) than among women born in Australia (0.9%).

Advice to EWG

The identified risk factors for diabetes in pregnancy do not differ from those identified in the previous review of the literature, with the exception of possible evidence on a threshold age at which risk increases.

Study ref	Design	LoE	N	Questions and studies	Findings	Comments
(NZ MoH 2014)	SLR	I	64 studies	<p>Question: <i>What risk factors are associated with increased risk of gestational diabetes?</i></p> <p>Studies: A total of 6 systematic reviews and 58 additional observational studies were identified. Comparison of studies is difficult as they differed in thresholds for the detection of hyperglycaemia in pregnancy, study design and definitions of outcomes. In general the overall quality of the evidence is considered to be very low.</p> <p>Summary: Some women with no known risk factors may still be diagnosed with gestational diabetes. Risk factor screening would fail to identify these women. For women with probable undiagnosed diabetes, the risk of adverse outcomes for mother and infant from waiting until 24–28 weeks' gestation for testing and diagnosis for gestational diabetes (as currently recommended) is unknown. Identification of women with diabetes early in pregnancy allows preventive measures to be commenced earlier.</p>	<p>A number of key risk factors suggest an increased risk of developing gestational diabetes.</p> <ul style="list-style-type: none"> • Increasing maternal age (≥ 25 years) • Increasing parity • Ethnicity (but not in isolation) • A family history of diabetes, in particular in a first degree relative • A previous pregnancy affected by GDM • Previous or current macrosomic or large for gestational age infant • Increasing BMI <p>There is probably interaction between risk factors that predisposes women to GDM rather than any single risk factor. The identification of women with increased risk factor(s) is likely to be of benefit if it is shown that preventive interventions are effective in reducing the incidence of GDM</p>	

3 What are the additional considerations for Aboriginal and Torres Strait Islander women?

Evidence summary

A systematic review (included in the New Zealand review) of evidence on the benefits of early screening for undiagnosed diabetes among indigenous women (in Australia, Canada, New Zealand and the United States) (Chamberlain et al 2013) found sufficient evidence that diabetes in pregnancy imposes a significant burden on indigenous women but insufficient evidence on current screening practice, acceptability of screening, efficacy and cost, availability of effective treatments and effective systems for follow-up after pregnancy.

Advice to EWG

Areas with insufficient evidence could be included as topics for future research.

Study ref	Design	LoE	N	Questions and findings	Individual studies	Comments
(NZ MoH 2014)	SLR	I	1 study	<p>Question: <i>What risk factors are associated with increased risk of gestational diabetes?</i></p> <p>Studies: A systematic review of evidence on the benefits of early screening for undiagnosed diabetes among indigenous women (in Australia, Canada, New Zealand and the United States)</p> <p>Summary: indigenous women are at higher risk of having undiagnosed type 2 diabetes</p>	<p>There is sufficient evidence describing the epidemiology of diabetes in pregnancy, demonstrating that it imposes a significant disease burden on indigenous women and their infants at birth and across the life course (n=120 studies) (Chamberlain et al 2013). Women with pre-existing type 2 diabetes have a higher risk than women who develop gestational diabetes during pregnancy.</p> <p>However, there was insufficient evidence to address the remaining five criteria, including: understanding current screening practice and rates (n=7); acceptability of screening (n=0); efficacy and cost of screening (n=3); availability of effective treatment after diagnosis (n=6); and effective systems for follow-up after pregnancy (n=5).</p>	

4 What are the additional considerations for women from culturally and linguistically diverse backgrounds?

Evidence summary

The New Zealand guidelines found that ethnicities with a high prevalence of diabetes included South Asian, Black Caribbean and Middle Eastern. Studies found differences in risk associated with ethnicity:

- *maternal age* — risk was higher for Black African, Black Caribbean and South Asian women at a younger age when compared to white European women
- *BMI* — higher risk was reported at BMIs of 22–24.0 among women of Asian background, 28–30 among Hispanic women, 34–36 among non-Hispanic white women and ≥ 37 among African American women
- *previous gestational diabetes* — the risk of gestational diabetes being diagnosed in the third pregnancy for women who had already had two gestational diabetes pregnancies was OR 35.0 (95%CI 14.8–83.1) for non-Hispanic White, OR 158.4 (95%CI 22.8–897) for non-Hispanic Black, OR 17.3 (95%CI 9.9–30.1) for Hispanic and OR 36.1 (95%CI 14.7–89) for Asian/Pacific Islander
- *migration* — studies noted an increased risk associated with being a migrant compared to being native to the country.

Advice to EWG

Incorporate new evidence into paragraph on ethnic origin in the section on assessing risk of diabetes.

Study ref	Design	LoE	N	Questions and studies	Findings	Comments
(NZ MoH 2014)	SLR	I	16 studies	<p>Question: What risk factors are associated with increased risk of gestational diabetes?</p> <p>Studies: One systematic review and 15 observational studies were identified that reported on ethnicity as a risk factor in the development of gestational diabetes. There was variation in the diagnostic tests used between the studies and in the variables used in adjusted models.</p> <p>Summary: risk factors associated with probable undiagnosed diabetes and gestational diabetes include:</p> <ul style="list-style-type: none"> • Family origin with a high prevalence of diabetes: <ul style="list-style-type: none"> — South Asian (specifically India, Pakistan, Bangladesh) — Black Caribbean — Middle Eastern (specifically Saudi Arabia, United Arab Emirates, Iraq, Jordan, Syria, Oman, Qatar, Kuwait, Lebanon, or Egypt) — Aboriginal, Pacific Island, Māori 	<p><i>Ethnicity and maternal age</i></p> <p>A number of inter-relationships were identified between race, BMI and maternal age such that a non-white pregnant woman aged 25 to 29 years has a similar risk of developing GDM as a White European woman of 40 years; about three to four fold greater than a White European age 20 to 24 years. The odds for developing gestational diabetes were also significantly higher in other racial groups but at a younger age (older than 25 years if they were Black African or Black Caribbean's and older than 20 years if they were South Asians)</p>	
					<p><i>Ethnicity and BMI</i></p> <p>One study reported that women of Asian or Filipina backgrounds had a higher risk of GDM at lower BMI levels (22 to 24.9kg/m²). The higher prevalence in other ethnicities was also detected at different BMI value: Hispanic (28 to 30 kg/m²), non-Hispanic white (34 to 36kg/m²) and African American (≥37kg/m²). The estimated population attributable risks suggested that 65% of cases of GDM in African American women and 23% in Asian women could be prevented if women were of normal BMI (<25kg/m²).</p>	

Study ref	Design	LoE	N	Questions and studies	Findings	Comments
					<p><i>Ethnicity and previous gestational diabetes</i></p> <p>Compared with women who had not been diagnosed with gestational diabetes in their first two pregnancies, the risk of GDM being diagnosed in the third pregnancy for women who had already had 2 GDM pregnancies was OR 35.0 (95%CI 14.8 to 83.1) for non-Hispanic White, OR 158.4 (95%CI 22.8 to 897) for non-Hispanic Black, OR 17.3 (95%CI 9.9 to 30.1) for Hispanic and OR 36.1 (95%CI 14.7 to 89) for Asian/Pacific Islander. Hispanics and Asian/Pacific Islanders had a much higher recurrence risk of GDM compared with White women.</p>	

Study ref	Design	LoE	N	Questions and studies	Findings	Comments
					<p><i>Migration</i></p> <p>A systematic review (24 observational studies; approximately 126,298 women) reporting the relationship between migration and the development of GDM identified migrant subgroups that showed greater risk of GDM compared with receiving countries.</p> <ul style="list-style-type: none"> • Caribbean (RR 3.03, 95%CI 2.26 to 4.05; 2 studies) • Unspecified African (probably North African) (RR 2.46, 95%CI 2.12 to 2.85; 4 studies) • European (RR 1.50, 95%CI 1.35 to 1.67; 3 studies) • Northern European (RR 1.21, 95%CI 1.03 to 1.42; 2 studies) <p>Three additional observational studies noted that there was an overall increased risk associated with being a migrant rather compared with being a national (born in the country).</p>	

Study ref	Design	LoE	N	Aim, setting, population, measurements	Results	Comments
(Hughes et al 2016b)	Cohort	III-2	11,580	<p>Aim: to compare inter-ethnic antenatal screening practices to examine whether the HbA1c test would be accessed by ethnicities most at risk of diabetes and to determine the prevalence of unrecognised type 2 diabetes and prediabetes in our pregnant population.</p> <p>Setting: Christchurch, New Zealand</p> <p>Population: Pregnant women attending for antenatal care.</p> <p>Methods: Utilising electronic databases, we matched maternal characteristics to first-antenatal bloods, HbA1c, and GDM tests (glucose challenge tests and oral glucose tolerance tests).</p>	<p>The combined prevalence of unrecognised type 2 diabetes and prediabetes by NZ criteria, HbA1c $\geq 5.9\%$ (41mmol/mol), was 2.1% in Europeans, Maori 4.7% IPR 2.59 (1.71, 3.93), Pacific People 9.5% IPR 4.76 (3.10, 7.30), and 'Others' 6.2% IPR 2.99 (2.19, 4.07). Applying these prevalence data to 2013 NZ national births data, routine antenatal HbA1c testing could have identified type 2 diabetes in 0.44% and prediabetes in 3.96% of women.</p>	

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