

## **HRC report: Screening for type 2 diabetes and pre-diabetes in early pregnancy. (STEP)**

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### **Abstract**

**Objective:** To determine whether a glycated haemoglobin (HbA1c) or random blood glucose (RBG) taken at the time of the first antenatal bloods can detect women with undiagnosed prediabetes or diabetes in early pregnancy.

**Methods:** Blood tests for diabetes were included with the routine first antenatal bloods. Women with a positive result were offered a further test to confirm diabetes and be given treatment as necessary. Women with known diabetes were excluded.

**Results:** Data collection and analysis is not yet completed. 17499 women were screened for diabetes with their first antenatal bloods and 1253 went on to have a 75g oral glucose tolerance test (GTT). In addition, 157 women with normal screening tests for diabetes had a GTT. A preliminary analysis of the raw data has been undertaken, but full analysis awaits completion of data collection. Using World Health Organisation (WHO) criteria 160 GTT met the threshold for prediabetes and 24 for diabetes during the course of the study. HbA1c  $\geq 5.6\%$  had a sensitivity of 77.3% and specificity of 42.2% of predicting diabetes using the WHO criteria.

**Impact:** Diabetes may go undetected for several years. In pregnancy, untreated maternal diabetes can cause problems for the baby including birth defects, delayed lung development, and obesity. Currently, women are offered testing for gestational (pregnancy) diabetes at 24-28 weeks of pregnancy. This means that women with undiagnosed pre-existing diabetes remain unrecognised until late pregnancy when treatment may be much less effective in reducing adverse pregnancy outcomes. Detection and prompt treatment of pre-existing diabetes in early pregnancy can reduce potential immediate and long-term harm to the baby and have a positive impact on maternal health.

### **Introduction**

Pregnancy may be playing a major role in the epidemic of type 2 diabetes via intra-uterine fetal programming.<sup>1-4</sup> Pregnant women with diabetes produce offspring with an increased risk of diabetes and obesity themselves and so the vicious cycle starts.<sup>5-6</sup> Early detection and treatment of diabetes in pregnancy may break this cycle of events. Since an estimated 50% of people with type 2 diabetes<sup>8</sup> (100,000 people in New Zealand) and many more pre-diabetes are undiagnosed, an early screening programme in pregnancy is warranted. Women with diabetes have increased risks of adverse pregnancy outcomes<sup>9-12</sup> and the risks are higher still for women with undiagnosed diabetes who are not identified and treated until late pregnancy. Research in New Zealand demonstrated that the perinatal mortality rate in the offspring of women with undiagnosed type 2 diabetes in pregnancy was higher than the rate in women with known type 1 or 2 diabetes.<sup>9</sup>

In New Zealand women are offered screening for gestational diabetes between 24-28 weeks gestation. This means that women with undiagnosed pre-existing diabetes, or marked glucose intolerance, remain unrecognised until a stage of pregnancy where treatment is likely to be much less effective in reducing adverse pregnancy outcomes. Early diagnosis of type 2 diabetes and pre-diabetes allows prompt treatment to improve pregnancy outcomes<sup>13</sup>, and also gives health professionals an excellent opportunity to educate women on lifestyle change and diabetes self-management that will reduce risks of long-term complications, which is especially relevant to the Maori and Pacific populations.

What screening test should be performed?

A simple test added to the 1<sup>st</sup> antenatal bloods would be ideal, but there are no good pregnancy data to address this issue. The World Health Organisation and International Diabetes Federation do not recommend any particular screening test.<sup>14</sup> A fasting blood glucose has a high false positive rate<sup>15-20</sup> and it is difficult to fast in the 1<sup>st</sup> trimester of pregnancy when morning sickness can be an issue. A random blood glucose is simpler, and although it is a relatively insensitive test<sup>20</sup>, the National Health and Medical Research Foundation of Australia recommends a cut-off of 5.5mmol/L for screening.<sup>21</sup> An HbA1c is also an easy add-on test, and a 'dose-dependent' relationship between HbA1c in early pregnancy and adverse pregnancy outcomes has been shown.<sup>22</sup> Outside of pregnancy HbA1c had the highest cost effectiveness in detecting previously undiagnosed diabetes.<sup>23-25</sup> A HbA1c cut-off of 6.1% has been proposed outside of pregnancy by many groups<sup>26</sup>, but the HbA1c is lower in pregnancy<sup>27</sup>. Advantages of HbA1c include a low intra-individual variability, it indicates chronic hyperglycaemia, and no fasting is required.<sup>26</sup>

More data are urgently required on screening for type 2 diabetes and pre-diabetes in pregnancy. HbA1c and random blood glucose are easy add-on tests to the 1<sup>st</sup> antenatal bloods, but cannot be recommended until more relevant data are collected. A 'Gestational Diabetes Technical Working Party' involving the Australasian Diabetes in Pregnancy Society, New Zealand College of Midwives, The New Zealand Society for the Study of Diabetes (NZSSD), The College of Obstetrics and Gynaecology, and representatives from diabetes and maternity consumer organisations, has written a technical report on gestational diabetes in New Zealand. In this report it is recommended that a pilot study needs to be initiated for screening pregnant women at high risk for undiagnosed type 2 diabetes, hence our STEP study.

Our aim is to determine whether HbA1c and / or a random blood glucose are useful antenatal screening tests to detect undiagnosed diabetes and prediabetes in early pregnancy. We also aim to determine whether screening only women with at least one risk factor for diabetes will improve specificity and be more cost effective without compromising sensitivity.

## Methods

This is an observational cohort study of pregnant women in Christchurch. A glycated haemoglobin (HbA1c) and random blood glucose (RBG) test were added to the first antenatal bloods and women were later invited to do a 75g two hour oral glucose tolerance test (GTT).

Main Outcome Measures:

- Sensitivity and specificity of random blood glucose, HbA1c, and a combination of both tests, in identifying women with diabetes or impaired glucose tolerance in early pregnancy.
- Sensitivity and specificity of each test, and a combination of both tests, in women with at least one risk factor for diabetes.

Ethical approval was granted by the Upper South B Ethics committee. Women were recruited over a 31 month period between February 1<sup>st</sup> 2008 and August 31<sup>st</sup> 2010. Data collection will continue until the last recruit has delivered her baby ~ May 2011. All pregnant women in the Christchurch area were eligible for enrolment, excluding only those women with known diabetes. Verbal consent was required for the first antenatal bloods and was gained by lead maternity carers (LMCs) and general practitioners. Written consent was required for the GTT and for researchers to access pregnancy information from the medical records. Women booked with a LMC of their choice and received standard care. During the course of the study if a woman was diagnosed with diabetes (using the current NZSSD criteria for gestational diabetes) she was referred to the Antenatal Diabetes Clinic at Christchurch Women's Hospital for specialist care.

Antenatal bloods were processed by three laboratories in Christchurch during the study period. All (Canterbury District Health Board, Medlab South and Southern Community Lab) used the same assay for determining HbA1c – Biorad Variant 2 HPLC, and RBG – enzymatic colourimetric testing. It is recognised there may be a 2% inter-laboratory error at the level of HbA1c cut off that we are interested in, this was deemed unimportant. In addition we felt that this method of utilising all the labs in Christchurch would best reflect the actual screening process should it be implemented on completion of our study. Where possible the RBG was taken in a fluorinated tube, but in some circumstances an EDTA tube was used. The results of the HbA1c and random glucose were sent to the study investigators with the patient details undisclosed, but with the laboratory reference number and LMC name cited. Full patient details and results were sent to the LMCs. An alert appeared on the LMCs copy of the results if a test was elevated advising that further action was recommended and that they should contact the study investigators. The study investigators also informed the LMC if one of their clients has an elevated result, and permission to approach their client with the patient information sheet and consent form was requested. Women with a HbA1c  $\geq 5.6\%$ , or a RBG  $\geq 5.5\text{mmol/L}$  were offered a GTT. In the last 12 months of the study all women were invited to do a GTT irrespective of their blood results with the aim of recruiting between 100-200 controls i.e. women with HbA1c  $< 5.6\%$  and a random glucose  $< 5.5\text{mmol/L}$ . Women approached for the control arm of the study were reimbursed for their time and travel expenses with a \$40 petrol or grocery voucher.

Demographic and pregnancy data were collected from the maternity records. In the event that records were unavailable the LMC was contacted for the relevant information. Demographic data included maternal age, ethnicity, pre-pregnancy weight and height, past history of polycystic ovarian syndrome, glucose intolerance, family history of diabetes, obstetric history, previous gestational diabetes, macrosomic baby, shoulder dystocia or unexplained stillbirth.

Potential for bias: During the study some LMCs were more likely to recruit women than others. Every effort was made to recruit as many women as possible by phone calls, faxes and reminder faxes to all the LMCs and GP practices.

**Statistical analysis:** Power of the study - the advice of a bio-statistician, Patrick Graham, was sought: It was predicted from the 2005 Christchurch Women's Hospital report that 5000 women deliver locally per annum. About one hundred and fifty women per annum would be diagnosed with gestational diabetes, of whom ~25-30% (37 to 45) would have pre-existing glucose intolerance or diabetes ('true positives'). The statistician concluded that no great statistical benefit would be gained from recruiting more than 105 true positives (105 women with diabetes or pre-diabetes). With 70 'true' positives the 95% confidence limits for a sensitivity of 90% are 82.9% to 97.0%. With 105 'true' positives the 95% confidence limits for a sensitivity of 90% are 84.2% to 95.7%. With 140 'true' positives the 95% confidence limits for a sensitivity of 90% are 85.0% to 94.9%.

This target was forecast to be met in 3 years based on previous clinic attendances at our hospital. However, in the first 7 month of the study we diagnosed 31 women with pre-diabetes or diabetes in early pregnancy, which meant that our target of 105 could be met by two years.

All data entered into the computer database is double checked to ensure accuracy. Associate Professor Elisabeth Wells, bio-statistician, will analyse the results. Statistical analysis will be undertaken using the statistical software package SAS. All tests will be two-tailed with  $P < 0.05$  considered significant. Categorical variables will be compared using the  $\chi^2$  test for linear association, if appropriate. Continuous variables, when assumptions of normality are met, will be analysed using analysis of variance and t-test where appropriate. ROCs will be calculated using sensitivity and 1-specificity (in %). Calculation of the area under the curve (AUC) will be performed with the SAS

ROC Curve function for the continuous variables (e.g. HbA1c). An AUC of < 0.50 is considered worthless, 0.60–0.69 poor, 0.70–0.79 fair, 0.80–0.89 good and 0.90–1 excellent. Optimal test characteristics will be considered to exist where sensitivity is equivalent to specificity.

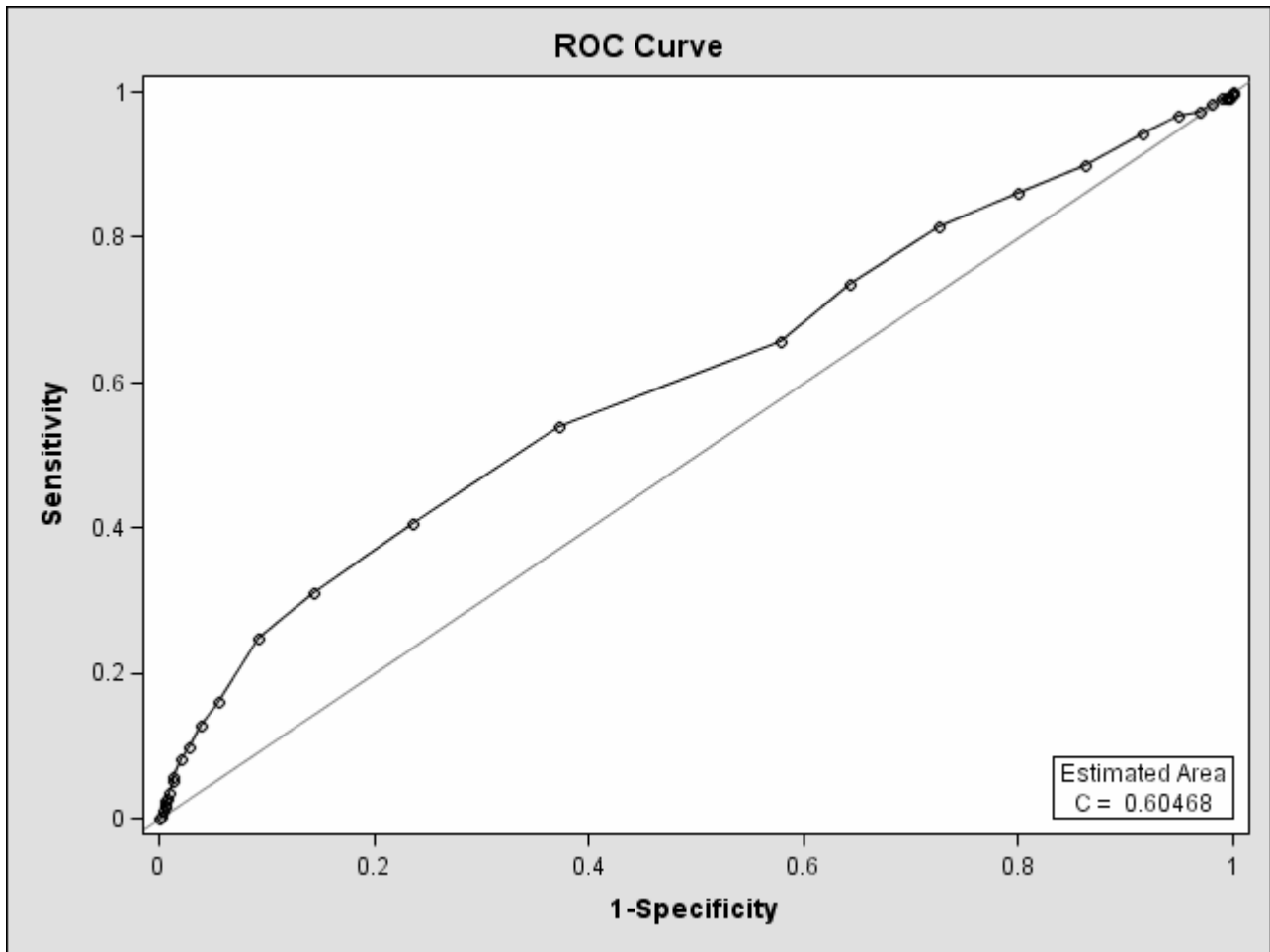
## Results

Data collection and entry are not yet complete; expected date of completion is July 2011. As a result we have undertaken only basic analysis of crude data for this report.

Participants: 17499 women had one or both of the HbA1c and RBG tests added to their first antenatal bloods. Of these about 20% were eligible for the 'abnormal' arm of the study of which approximately 30% underwent a GTT (n = 1253). Only ~10% (n = 157) of those approached consented for the normal arm of the study. The main reasons for non-participation included: first antenatal bloods taken when not actually pregnant, failed pregnancy, planned termination of pregnancy, declined participation, and known diabetes. Demographic data and pregnancy outcome data are not yet available to report.

The following results show the specificity and sensitivity of HbA1c and RBG at predicting a positive GTT at **any stage** of pregnancy. This is not one of our outcome measures, we need to enter all the expected date of deliveries into the database and remove women who had a GTT beyond 20 weeks gestation from this analysis to address our outcome measure. In addition, we are not yet able to address our second aim until all the demographic data are collected and entered into the data base. For the final analysis we will calculate the sensitivity and specificity of HbA1c or RBG compared to a positive GTT using both the World Health Organisation (WHO) and American Diabetes Association (ADA) criteria for impaired glucose tolerance, impaired fasting glycaemia and diabetes, and the NZSSD and HAPO (Hyperglycaemia and Pregnancy Outcomes Trial) criteria for diagnosing gestational diabetes.

The sensitivity and specificity of HbA1c  $\geq 5.6\%$  taken with the first antenatal bloods at predicting an abnormal GTT using the WHO guidelines at **any stage** of pregnancy are 62.8% and 42.3% respectively (please bear in mind that this result is on preliminary data and is likely to be revised). For predicting frank diabetes using the WHO criteria the sensitivity and specificity of HbA1c  $\geq 5.6\%$  are 77.3% and 42.2% respectively. Similarly the sensitivity and specificity of HbA1c  $\geq 5.6\%$  are 61.3% and 42.2% respectively using the NZSSD criteria for GDM and 65.6% and 42.2% respectively using the HAPO criteria for GDM. The ROC curves are meaningless at this stage until the data are finalised, however here is one demonstrating HbA1c against GTT using the HAPO cut-offs for diagnosing GDM.



## Discussion

The key results we will publish are:

- Sensitivity and specificity of random blood glucose, HbA1c, and a combination of both tests, in identifying women with diabetes or impaired glucose tolerance in early pregnancy.
- Sensitivity and specificity of each test, and a combination of both tests, in women with at least one risk factor for diabetes.

The limitations of the study include potential for recruitment bias given that we were reliant on LMCs and GPs to provide the contact information for potential recruits. In some cases this information was incorrect and we were unable to make contact. In addition, we had no control over when women actually went for their GTTs and it is possible that many waited until after they were 20 weeks pregnant.

The results of our study should be generalisable to New Zealand as a whole given that women of a wide range of ages and ethnicities had the HbA1c and RBG tests taken. We are yet to analyse the demographics of the women who underwent a GTT. This study will evaluate whether HbA1c and / or a RBG should be added to the routine 1<sup>st</sup> antenatal bloods in New Zealand, or to just those women with known risk factors for diabetes. It will demonstrate the practical feasibility of a screening programme and in addition it will provide important information on the true incidence of type 2 diabetes in pregnancy.

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