Prediabetes and pregnancy:
Early pregnancy glycated haemoglobin identifies Australian Aboriginal women with high-risk of gestational diabetes mellitus and adverse perinatal outcomes

What do we already know?

Gestational diabetes mellitus (GDM) refers to high blood glucose levels during pregnancy. It is commonly detected later in pregnancy after blood sugars start to rise midway through pregnancy in women without pre-existing blood sugar problems ('standard GDM'). However, some women diagnosed with GDM may have unrecognised prediabetes (high blood glucose levels which may turn into type 2 diabetes later in life). GDM and prediabetes in pregnant women can cause problems like big babies with complicated births, and perinatal complications. Detecting prediabetes and optimising blood glucose before and during pregnancy may help stop these problems.

Glycated haemoglobin (HbA_{1c}) is used to diagnose type 2 diabetes (≥6.5%) and prediabetes (Kimberley protocol: 5.7%-6.4%; National protocol: 6.0-6.4%) outside of pregnancy. In pregnancy the HbA_{1c} is less reliable. The amount of HbA_{1c} women have in their blood normally drops, but it can also rise in women who have iron deficiency anaemia (low iron stores and haemoglobin levels). Because of these unpredictable changes, HbA_{1c} is only recommended for detection of overt diabetes in pregnancy (likely type 2 diabetes). There is no consensus on early HbA_{1c} thresholds to detect clinically significant glucose levels that would require management:

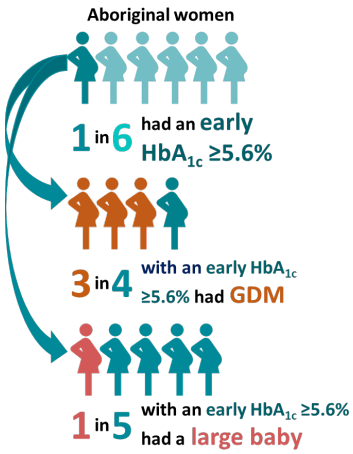
National guideline:	Threshold and classification for management:
NHMRC (2017) & RACGP (2020)	Early pregnancy: **HbA_{1c} ≥5.9% - hyperglycaemia in early pregnancy**
ADIPS (2014) & RANZCOG (2017)	Any gestation: **HbA_{1c} ≥6.5% - diabetes mellitus in pregnancy**
ADIPS (2020) COVID-19 guideline	Early pregnancy: **HbA_{1c} 5.9-6.4% - GDM (temporary guideline)**

NHMRC, National Health and Medical Research Council; RACGP, The Royal Australian College of General Practitioners; ADIPS, The Australasian Diabetes in Pregnancy Society; RANZCOG, The Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

There is also no recommendation for lower HbA_{1c} levels to identify prediabetes in pregnancy. The recommended test for GDM (which also detects prediabetes in pregnancy) is an oral glucose tolerance test (OGTT), also known as the sugar drink test. This involves fasting overnight and having three blood samples collected over two hours. The OGTT is used to test for standard GDM in all women **later in pregnancy** (24- and 28-weeks gestation). Additionally, women who have high risk for diabetes (including Aboriginal women and women who are obese) are recommended to have an extra OGTT **early in pregnancy** (<20-weeks gestation). Our first paper showed that it can be difficult to get everyone to do this test.

What does this research show?

The **ORCHID Study** (Optimisation of Rural Clinical and Haematological Indicators of Diabetes in pregnancy) was designed to help simplify screening for GDM in rural and remote WA. We looked at early HbA_{1c} levels (<20-weeks gestation) for 396 ORCHID study participants who also had an OGTT after 24-weeks gestation. The aim was to find a HbA_{1c} cut-point that could be used to help predict future GDM.



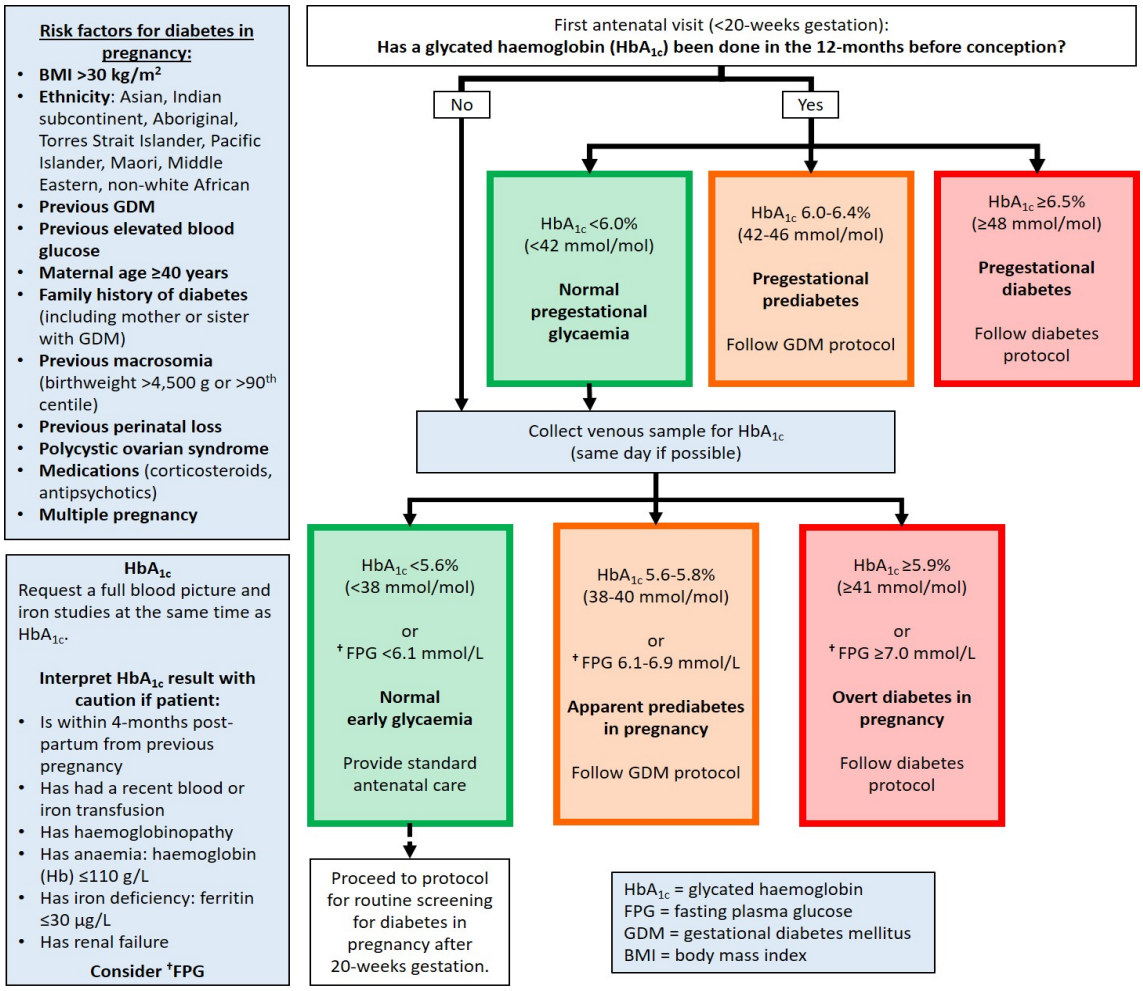
We found that the best early HbA_{1c} value for predicting GDM in Aboriginal women was ≥5.6% (specificity: 93.9%). Almost three-quarters (71.4%) of Aboriginal women with early HbA_{1c} ≥5.6% went on to have a positive OGTT.
We think these women had prediabetes going into pregnancy.

There were clear differences between Aboriginal and non-Aboriginal women: 16.3% v 5.2% had elevated HbA_{1c} (pre-pregnancy prediabetes) whereas 12.4% v 29.6% developed GDM during pregnancy. This suggests **fewer non-Aboriginal women had prediabetes going into pregnancy compared to Aboriginal women.**

Overall, in 466 ORCHID study participants with an early HbA_{1c} (Aboriginal & non-Aboriginal), the risk of having a large baby was twice as high in women with an early HbA_{1c} ≥5.6% compared to women with an early HbA_{1c} <5.6% and without GDM (21.4% v 10.5%). This suggests that **women with prediabetes in early pregnancy have high-risk for a large baby.**

What does this mean for clinical practice?

We suggest measurement of HbA_{1c} at first antenatal visit for all Aboriginal women. There has not yet been much published research into the benefits of early intervention for women with prediabetes in pregnancy, however results of a New Zealand study of Prediabetes in pregnancy, can early INtervention improve Outcomes (PINTO), are due later in 2021, which should help guide recommendations. We are interested in discussing the clinical implications of our findings with health professionals and Aboriginal women and to co-design a culturally appropriate intervention for women with prediabetes in pregnancy. This will be critical to promote healthy changes before and during pregnancy to minimise the impacts of high glucose on mothers and babies.



Future research

In the Kimberley, all women have been offered an early HbA_{1c} at their first antenatal visit since 2017 to check for pre-existing diabetes. As part of the Kimberley Aboriginal Medical Services & Rural Clinical School of WA research collaboration, we are currently looking at outcomes for Kimberley women who delivered their babies between 2018 and 2021. This will give us a larger, more representative of group of Kimberley women to validate the early HbA_{1c} ≥5.6% threshold.

We would like to thank all health service staff who assisted in completing this project and the health services that agreed to participate. This project is a collaboration between Rural Clinical School of WA, Kimberley Aboriginal Medical Services, WA Country Health Services and this part was funded through grants from RCSWA, Lishman Health Foundation and Diabetes Australia. Click here to read this ORCHID study publication and other plain language statements. If you have any questions or comments, please direct them to ORCHID Study Chief Investigator, A/Prof Julia Marley.

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