Protocol Review: Evidence used and rationale

Protocol name: Diabetes in pregnancy

Rationale: The current Kimberley Diabetes in pregnancy protocol was overdue for review – last reviewed 2011. Clinicians in the region had noted significant change in practice both nationally and regionally so a working group was formed. The need for a simple user friendly protocol was identified for use in clinical situation and by the clinician not familiar with care of the diabetic or gestation diabetic woman in pregnancy. The creation of a background/rationale document was felt to be necessary by the working group due to the large volume of background information and regional difference and contacts needed to be included while still maintaining the aim of a simple reference guideline.

Diabetes in pregnancy refers to GDM and pre-existing diabetes, all of which can lead to a range of complications for the mother and child (see Box 1). The diagnosis of diabetes in pregnancy will include those women with previously undiagnosed abnormalities of glucose tolerance, as well as women with glucose abnormalities related to the pregnancy alone.

Box 1: Complications associated with diabetes in pregnancy

Risks for the baby include: miscarriage, stillbirth, congenital malformations and respiratory distress. There is also increased risk of obesity, impaired glucose tolerance and type 2 diabetes in early adulthood.

Risks for the mother include: miscarriage, pre-eclampsia, induced labour, pre-term birth, caesarean section, and first appearance or progression of complications including those associated with kidney, eye and cardiovascular diseases. For mothers with GDM there is a risk of recurrent GDM in subsequent pregnancies and progression from GDM to type 2 diabetes.

Burrow. S, & Ride. K. (2016)

Short term implications for the mother and baby caused by DIP are not the only leading concern. There is increasing evidence of the adverse intrauterine effects on the baby to cause increased future risks of diabetes and obesity. This further perpetuates the vicious cycle of “diabesity” in future generations adding to the already growing epidemic. Optimal treatment of DIP can reduce the short term complications for both the baby and mother (Maple-Brown et al., 2012).

A major national survey, called the *2012-2013 National Aboriginal and Torres Strait Islander Health Survey,* found:

- National prevalence of diabetes (type 1, type 2 or high sugar levels) among ATSI people range from 8.6% to 11.1%
- The prevalence among ATSI people was highest in the Northern Territory at 12%, and lowest in Tasmania at 3.8%, with 10% in Western Australia, 8.9% in South Australia, 8.3% in Queensland, 8.1% in New South Wales, 7.6% in the Australian Capital Territory, and 7.1% in Victoria.
- Diabetes/high sugar levels were more common among Indigenous people living in remote areas (that is, communities/small towns) (around 1 in 11) than among those living in non-remote areas (that is, big towns/cities) (around 1 in 20)
- Diabetes/high sugar levels were more than 3 times more common among Indigenous people than among non-Indigenous people
- The difference of diabetes/high sugar levels between Indigenous and non-Indigenous females greater than the difference between Indigenous and non-Indigenous males
- Indigenous people were more likely to get diabetes at younger ages than non-Indigenous people.

Age group (years)	Indigenous people %	Non-Indigenous people %	Ratio
15-24	1.4	NA	NA
25-34	5.3	1.1	4.8
35-44	11	2.8	4.0
45-54	23	5.6	4.2
55+	40	14	2.9

Table 1: Diabetes - percentages of people reporting diabetes/high sugar levels as a 'long-term health condition', by Indigenous status, and Indigenous:non-Indigenous ratios, Australia, 2012-13

There have not been many studies of diabetes in pregnancy, but one study from the Northern Territory found:

- Around 1 in 16 Indigenous women developed gestational diabetes
- Around 1 in 25 non-Indigenous women developed gestational diabetes

After taking account of the fact that Indigenous women tend to have babies at younger ages than non-Indigenous women, the level of gestational diabetes for Indigenous women was more than twice that of non-Indigenous women.

For these reason a high prevalence of diabetes in pregnancy is treated in the Kimberley in a relatively small obstetric population. This combined with a mobile population spread across a region that is 423,517 km² with patients often difficult to follow up meant that some changes are needed to state guidelines – KEMH guidelines.

A new study (Nini Helthiwan) into maternal and child health was commenced in the Kimberley in 2015/2016. A review of the maternal and child health protocols to reflect the best evidence was requested in order to inform that study.

Initial Diabetes in Pregnancy Protocol Working Group:
KAMS: Sarah Woodland (GP and protocol team leader 2016), Chevaun Howard (Obstetric GP - KAMS),

WACHS Obstetrics: Head writer – Kristy Newett (Clinical and Research Midwife - Nini Helthiwan Project/WACHS), Wendy Hughes (Director of Obstetrics & Gynaecology), Jared Watts (Regional Obstetrician) Pam Walker (Clinical Midwife – WACHS/Midwife Group Practice), Penny Wilson (Obstetric GP – WACHS), Samantha Peterson (Nurse Practitioner- WACHS – Fitzroy Crossing)

WACHS Physician team: Justin Barton (Physician registrar), Jaye Martin (Regional Physician)

Boab Health Diabetes Educator: Bernadette O'Brien (West Kimberley), Mandy Harding (East Kimberley)

Further review/significant input from: Emma Griffiths (GP and protocol co-ordinator-2015), Jaye Martin (Regional Physician), Emma Robinson (Boab Dietitian)

Discussion points:

Use of HbA1c in pregnancy:

Currently there is no validated evidence or national recommendation or guidelines on use of HbA1c in pregnancy.

If being Aboriginal or TSI is their only risk factor, women do not need an early GTT, but if not up to date with routine screening then screening for pre-existing diabetes with HbA1c should be performed in first trimester. Refer to T2DM protocol for further information http://103.18.109.102/~kamscorg/wp-content/uploads/2016/11/Diabetes-Type-II-August-2015.pdf. This test has been validated for screening for undiagnosed diabetes in the non-pregnant population, and is supported in the first trimester by the American Diabetes Association and by the Australasian Diabetes in Pregnancy Society (ADIPS).

An abnormal HbA1c in the first trimester is diagnostic of pre-existing diabetes (See T2DM protocol for interpretation of HbA1c results).

Interpretation of HbA1c in second and third trimester is less well defined, due to the change in turnover of red blood cells.

Until research has identified the utility of HbA1c, the diagnosis of GDM is still based on OGTT results. An HbA1c result of ≥ 5.7% (42 mmol/mol) (equivalent to a diagnosis of pre-diabetes in the non –pregnant population) should be monitored as per GDM and treatment instituted as indicated, and ideally followed up with an OGTT to guide diagnosis. Research is currently being undertaken to provide clearer guidance on the use of HbA1c cut points in GDM screening. The ORCHID study is currently being undertaken in WA to assess the possibility of this.

King Edward Memorial Hospital (KEMH) guidelines recommend testing HbA1c every trimester from diagnosis of pregnancy as this may possibly help with correlating HbA1c values with glycaemic profiles for the future. Also this may help give insight into the adequacy of control, especially when glycaemic profile not being performed. Although research has demonstrated HbA1c in first trimester seems to be the most predictive of perinatal outcomes. (Wong, Chong, Mediratta & Jalaludin, 2017).

Pre Conception

The National Diabetes in Pregnancy Advisory Council set the optimal maintenance pre conception glycaemic targets of <7% but do state there is evidence that the HbA1c should be maintained within the normal range as if possible, whilst avoiding hypoglycaemia. NICE recommend women with diabetes who are planning to become pregnant to aim to keep their HbA1c level below 48 mmol/mol (6.5%), also noting only if this is achievable without causing problematic hypoglycaemia. KEMH also advise HbA1c <7% over three months preconception with ADIPS patient handout available on their site http://www.kemh.health.wa.gov.au/services/diabetes/adips.pdf

BMI cut offs for delivery in Kimberley hospitals:

Guidelines for BMI cut offs to deliver in Broome hospital were requested by staff during the process of reviewing this guideline. The 2016 WACHS Kimberley Obstetric Patient Referral – Admission and Transfer Criteria to a Higher or Tertiary Level Care Procedure for Birthing Sites policy addresses this with the following:

- BMI is preferably measured in first trimester
- If BMI in the 1st trimester is >40, women are to be advised that it would be safer to birth outside of the Kimberley, unless there are particularly favourable features such as previous uncomplicated Kimberley births at the same, or close to the same BMI. In this circumstance, the Regional Obstetrician and anaesthetic DMO group must be consulted.
- BMI over 34-40 in first trimester is to be reviewed by both the anaesthetic DMO and specialist obstetrician and discussed collaboratively
- The aim in all cases, is to provide an early decision to give the woman consistent advice as to place of birth as early in the pregnancy as possible.
- Individual factors will always need to be taken into consideration, and the management of any individual woman will depend on the skill set of the available anaesthetic and obstetric doctors working at the hospital in question. These figures should be used to guide referral.

In addition these are recommendations from the working group:

- Kununurra and Derby, will have a lower threshold for transferring higher BMI's but many women whose BMI between 34-40 will be able to birth in Broome
- Diabetics requiring insulin, or where control is considered suboptimal, whatever their BMI, will be advised to deliver in Broome and sometimes KEMH because more intensive neonatal services are available.

Indications for medical treatment:

As a general principle all patients should be offered 1-2 weeks for diet and exercise before initiation of metformin – if however the clinical practitioner believes that this will be ineffective due to high baseline BSL eg. > 10mmol/L then metformin can be initiated earlier. – This is included in the regional protocol as 1-2 weekly review is often not possible due to both patient and system factors – i.e. schedule of servicing of communities, patients' frequent travel within region/between communities due to family/cultural commitments and increase frequency of high severity of diabetes at time of diagnosis.

Metformin use in pregnancy:

Research has demonstrated that the use of metformin gives comparable outcomes to insulin in the management of women with gestational diabetes (see resources).

Metformin use in GDM can:

- Reduce severe neonatal hypoglycaemia.
- Reduce weight gain during pregnancy and promote weight loss after delivery.

Women preferred treatment with metformin compared to treatment with insulin. Follow up of the offspring to date has shown no difference between those whose mothers were treated with insulin and those whose mothers were treated with metformin.

Long-term follow-up of children born to mothers with gestational diabetes who took metformin during pregnancy has shown that, if anything, the children at 2 years have less abdominal fat than children whose mothers had been managed with insulin alone.

The use of metformin in pregnancy is not currently endorsed by regulatory authorities or professional bodies, including the Australasian Diabetes in Pregnancy Society (ADIPS). Although no adverse effects have been demonstrated to date, metformin does cross the placenta, leading authorities to be very cautious in their recommendations.

Metformin can be considered for use in women who have failed non-drug treatments and who either refuse or are unable to take insulin. The mother should be educated about the potential risks, benefits and areas of uncertainty so that an informed decision can be made.

Start with standard metformin 500 mg daily, depending on the glucose profile, and increasing weekly as required with 2000mg as maximum dose.

Long acting (XR) metformin may be considered, particularly at night for those with fasting hyperglycaemia

Aspirin

Pre-existing diabetes can put women at a higher risk of developing pre-eclampsia (PE). Early symptoms include high blood pressure and proteinuria and if left untreated, eclampsia can develop which is life threatening for both mother and baby. Perinatal risks of maternal hypertension also include fetal growth restriction (FGR) and premature birth. In 2014, the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guidelines were updated with key recommendations to include use of aspirin to reduce the risk of PE in moderate to high risk women.

A meta-analysis of RCTs comparing the effect of daily aspirin or placebo during pregnancy to prevent pre-eclampsia published in 2017 concludes:

The effectiveness of aspirin is not only dependent on the gestational age at initiation of treatment but also on *the dose of the drug* which is supported by the results of a previous meta-analysis, from the Cochrane Database, which reported a greater reduction in the risk of PE with the use of aspirin >75 mg/d (17 trials) or the combination of aspirin >75 mg/d and dipyridamole (5 trials;) compared to aspirin <75 mg/d (21 trials). Another meta-analysis (13 trials) reported that the effect of aspirin for the prevention of FGR was greater when treatment started at <16 weeks' gestation and the dose 100-150 mg/d rather than 50-80 mg/d.

So although the authors are unable to determine the optimal dose in this analysis as the No. of participants per sub-groups is too small, overall when 100mg daily was commenced under 16/40 there were significant reductions of PE or FGR as the commonly used dose of 81mg has no appreciable effect on platelet function in up to one third of women. (Roberge, et al, 2017)

Post-Partum

Most women with gestational diabetes revert to normoglycaemia at the time of the birth and do not require medication in the postnatal period. Checking a random BGL the day after the birth with a repeat 4 point BGL (fasting and 2 hours post meals for three meals) once on the day prior to discharge will determine if further management is required. Blood glucose monitoring should be ceased if BGL within the

normal range (KEMH, 2012). Women with pre-existing diabetes should be referred back to their routine diabetes care arrangements and this should be documented on the medical discharge summary from the birthing hospital.

Although National and International guidelines suggest women with GDM should be followed up with an oral glucose test at 6 -12 weeks postpartum, our Kimberley guidelines recommend testing with HbA1c at four months postpartum. This is in accordance with the Kimberley Type 2 Diabetes protocol screening in the adult non-pregnant population therefore by four months postpartum the red blood cells have returned to normal and should not return an artificially low result. In conjunction with NICE guidelines, do not routinely offer a 75 g 2-hour OGTT at the 6-8 postnatal check, instead offering screening for T2DM with an annual HbA1c test to women who were diagnosed with gestational diabetes and who have a normal HbA1c test postpartum. *Practice Point*: This HbA1c test for mothers could also be encompassed with the 4 month old universal child health check visit that is required for baby.

RESOURCES AND REFERENCES:

Guidelines (Government, College and Hospital):

- Australasian Diabetes in Pregnancy Society. (2014). *ADIPS Consensus Guidelines for the Testing and Diagnosis of Hyperglycaemia in Pregnancy in Australia and New Zealand*. Retrieved from http://adips.org/downloads/2014ADIPSGDMGuidelinesV18.11.2014_000.pdf

- Australasian Diabetes in Pregnancy Society. (2005).*The Australasian Diabetes in Pregnancy Society Consensus Guidelines for the management of patients with Type 1 and Type 2 Diabetes in Relation to Pregnancy*. Retrieved from http://adips.org/downloads/adips_pregdm_guidelines.pdf

- Department of Health. (2014). *National Antenatal Care Guidelines. Module 2*. Retrieved from http://www.health.gov.au/internet/main/publishing.nsf/content/015FBFDD266795DBCA257BF0001A0547/$File/Antenatal-care-module2_Clinical-Practice-Guidelines.pdf

- National Health and Medical Research Council. (2013). *Australian Dietary Guidelines*. Canberra: National Health and Medical Research Council.

- NSW Government Food Authority. (2016). *Food safety During Pregnancy*. Retrieved from http://www.foodauthority.nsw.gov.au/_Documents/foodsafetyandyou/pregnancy_brochure.pdf

KEMH guidelines:

- Diabetes in Pregnancy : Screening for: http://www.kemh.health.wa.gov.au/development/manuals/O&G_guidelines/sectionb/3/b3.1.1.pdf revised 2012.

- Women with a body mass index above 40: Management of pregnancy and childbirth in: http://www.kemh.health.wa.gov.au/development/manuals/O&G_guidelines/sectionb/2/b2.21.pdf, reviewed May 2014

- Neonatal management of existing maternal conditions: Maternal vitamin D deficiency: http://www.kemh.health.wa.gov.au/development/manuals/O&G_guidelines/sectionp/alpha/p_cholecalciferol.pdf, updated 2013.

- Diabetes in Pregnancy: Postnatal Care: http://www.kemh.health.wa.gov.au/development/manuals/O&G_guidelines/sectionb/3/b3.1.14.pdf reviewed 2015.

- Can I have a healthy baby? http://www.kemh.health.wa.gov.au/services/diabetes/adips.pdf

NICE: National Institute for Health and Care Excellence guidelines:

- Diabetes in pregnancy: management from preconception to the postnatal period https://www.nice.org.uk/guidance/ng3/chapter/1-Recommendations#postnatal-care-2

RANZCOG guidelines:

- Vitamin and Mineral Supplementation in Pregnancy: https://www.ranzcog.edu.au/doc/vitamin-and-mineral-supplementation-in-pregnancy.html, updated May 2015.
- Management of Obesity in Pregnancy: https://www.ranzcog.edu.au/doc/management-of-obesity-in-pregnancy.html
- Diagnosis of Gestational Diabetes Mellitus (GDM) and Diabetes Mellitus in Pregnancy https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Diagnosis-of-GDM-(C-Obs-7)-Review-July-2014.pdf?ext=.pdf

Royal College of Obstetricians and Gynaecologists:

- Royal College of Obstetricians and Gynaecologists: Recreational exercise and pregnancy – information for you, https://www.rcog.org.uk/globalassets/documents/patients/patient-information-leaflets/pregnancy/recreational-exercise-and-pregnancy.pdf, September 2006.

Society of Obstetric Medicine of Australia and New Zealand:

- Guidelines for the Management of Hypertensive Disorders of Pregnancy (2014) https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/SOMANZ-Hypertension-Pregnancy-Guideline-April-2014.pdf?ext=.pdf

World Health Organization (WHO) guidelines:

- World Health Organization (2013) Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf
- World Health Organization (2011) Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus http://www.who.int/diabetes/publications/report-hba1c_2011.pdf

Systematic Reviews and Journal Articles:

Bartsch, E., Park, A., Kingdom, J. & Ray, J. (2015). Risk Threshold for Starting Low Dose Aspirin in Pregnancy to Prevent Preeclampsia: An Opportunity at a Low Cost. *Plos One*. DOI: 10.1371/journal.pone.0116296

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Helou, A., Walker, S., Stewart, K., & George, J. (2017). Management of pregnancies complicated by hypertensive disorders of pregnancy: Could we do better? *Australian and New Zealand Journal of Obstetrics and Gynaecology.* DOI: 10.1111/ajo.12499

Maple-Brown, L., Brown, A., Lynn, I., Connors, C., Whitbread, C., O'Dea, K., Oats, J., McIntyre, D., Shaw, J., & Zimmet, P. (2012). Pregnancy and Adverse Neonatal Diabetes Outcomes in Remote Australia (PANDORA) Study. Cited in *Publication of the Chronic Diseases Network* VOLUME 24, ISSUE 4, http://digitallibrary.health.nt.gov.au/prodjspui/bitstream/10137/517/14/Chronicle%2c%20Vol%2024%20Issue%204%2c%20December%202012.pdf

Markey, P., Weeramanthri, T., & Guthridge, S. (1996). Diabetes in the Northern Territory. Darwin: Diabetes Australia, https://www.healthinfonet.ecu.edu.au/uploads/docs/diabetes-pl-review.pdf

Moses, R., Wong, V., Wong, K., Lambert, K., Morris, G. & San Gil, F. (2016). The prevalence of hyperglycaemia in pregnancy in Australia. *Australian and New Zealand Journal of Obstetrics and Gynaecology* ; *56*: 341–345 DOI: 10.1111/ajo.12447

Ota, E., Hori, H., Mori, R., Tobe-Gai, R., & Farrar, D. (2015). Antenatal dietary education and supplementation to increase energy and protein intake, *Cochrane Database of Systematic Reviews*, DOI: 10.1002/14651858.CD000032.pub3.

Ramakrishnan, U., Grant, F., Goldenberg, T., Zongrone, A., & Martorell, R. (2012). Effect of women's nutrition before and during early pregnancy on maternal and infant outcomes: a systematic review. *Paediatr Perinat Epidemiol.* Jul 26 Suppl 1:285-301

Roberge, S., Nicolaides, K., Demers, S., Hyett, J.,Chaillet,N., & Bujold, E. (2017). The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. *American Journal of Obstetrics & Gynecology.* 216: 110-120. http://dx.doi.org/10.1016/j.ajog.2016.09.076

Rolnik, D., Wright, D., Poon, L., O'Gorman, N., Syngelaki, A., de Paco Matallana, C., …Nicolaides, K. (2017). Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *The New England Journal of Medicine*. DOI:10.1056/NEJMoa1704559

Sarma, A., & Scott, N. (2016). Aspirin Use in Women: Current Perspectives and Future Directions. *Current Atherosclerosis Reports*.

Scott, P., Zhang, Y., & Nolan, C. (2016). The gestational diabetes tsunami: Can we survive it? *Australian and New Zealand Journal of Obstetrics and Gynaecology*. *56*: 333–335 DOI: 10.1111/ajo.12502

Vincent, W., Wong, V., Chong, S., Mediratta, S., & Jalaludin, B. (2017). Measuring glycated haemoglobin in women with gestational diabetes mellitus: How useful is it? *Australian and New Zealand Journal of Obstetrics and Gynaecology*. 57: 260-265. DOI: 10.1111/ajo.12511

Resources:

Healthy Eating during your Pregnancy:
https://www.eatforhealth.gov.au/sites/default/files/files/the_guidelines/n55h_healthy_eating_during_pregnancy.pdf

Carbohydrates and Glycaemic Index:
http://admin.bakeridi.edu.au/Assets/Files/Carbs%20&%20Glycaemic%20Fact%20SHEET.pdf

Plating it up: The Portion Guide:
http://admin.bakeridi.edu.au/Assets/Files/Plate%20Portion%20Guide%20(2015).pdf

Healthy Eating for Gestational Diabetes: https://baker.edu.au/-/media/Documents/fact-sheets/BakerIDI-factsheet-healthy-eating-for-gestational-diabetes.ashx?la=en

Pregnancy and Diabetes:
https://www.health.qld.gov.au/__data/assets/pdf_file/0026/161792/pregnancy_diabetes.pdf

Eating for Gestational Diabetes: http://www.diabetesqld.org.au/media/308373/eating_for_gestational_diabetes.pdf

Nutrition for Diabetes in Pregnancy: http://www.healthylivingnt.org.au/content/?action=getfile&id=711