Protocol Review: Evidence used and rationale

Protocol name: Iron deficiency anaemia and iron in pregnancy

Rationale: The current Antenatal protocol, which contains sections on iron and anaemia in pregnancy, was overdue for review. Clinicians in the region have requested greater detail in the Antenatal protocol, therefore the decision was made in the working group to separate the protocol into multiple components, one of which is the new "Iron and anaemia in pregnancy" protocol.

A new study (Nini Helthiwan) into maternal and child health is due to commence 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.
Last updated: 2012

Initial Working Group:
KAMS: Emma Griffiths (GP and Protocol Coordinator), Janet de San Miguel (Regional Coordinator Maternal & Child Health), Donna Stephen (Nini Helthiwan Project Manager), Rebekah Ledingham (Obstetric GP)

WACHS Obstetrics: Wendy Hughes (Regional Obstetrician), Pip Gale (Senior Obstetrics Registrar)

WACHS KPHU: Melissa Williams (Maternal and Child Health Coordinator)

Further review from: Emma Robinson (Paediatric Nutritionist), Kimberley Aboriginal Health Planning Forum (KAHPF) Maternal and Child Health Sub-committee

Discussion points:

Cut offs of ferritin to indicate iron deficiency:
Normal ranges for ferritin are poorly described in pregnancy. Where bone marrow biopsy has been performed in second and third trimesters of pregnancy as a gold standard, a ferritin of less than 30 was 90% sensitive and 85% specific for absent iron in the marrow (Van Den Proek). A ferritin of 70 has been estimated to be equivalent to an iron reserve of 500mg, which "nearly balances the net iron loss during pregnancy" (Milman 2011).

In an otherwise well population of women, the 97.5th centile for ferritin (ug/l) was 106.4 in first trimester, dropping to a low point of 39 in weeks 28 - 31, and rising to 43.5 by weeks 34 – 38. These upper limits have been used to estimate the normal haemodilution that might be seen in a healthy pregnancy with adequate iron reserves.
A ferritin of 70 is therefore used as a cut-off first trimester to identify women who do not require iron supplementation in pregnancy, with estimates for second and third trimester based on some allowable measure of haemodilution. There is research currently underway in the Kimberley which will examine the prevalence and management of iron deficiency in pregnancy and the effects on infant outcomes, including neurodevelopmental status and anaemia.

Eosinophilia, strongyloidiasis and deworming in pregnancy:

Eosinophilia
Eosinophilia may be an indication of parasitic infection, however there are other causes of eosinophilia, and eosinophils may be elevated for some time after treatment of an infectious cause. Other causes of eosinophilia include drug reactions and allergies. Eosinophils may be normal despite having an active parasitic infection, and eosinophilia can be suppressed by concurrent bacterial infection or immunosuppression, Eosinophilia is thus neither sensitive nor specific for parasitic infection. Extremely high eosinophil counts require further investigation and may indicate a neoplastic condition.

Chronic strongyloidiasis is the most important parasitic condition to treat in the Kimberley setting. Isolated eosinophilia is an indication for further investigation with strongyloides serology (test and treat) or treatment for strongyloidiasis (empirical treatment) depending on the underlying risk factors

for complicated / disseminated strongyloidiasis. In the non-pregnant population these risk factors predominantly relate to immunosuppression, including steroid therapy, solid organ transplantation, diabetes and renal disease. There is documented evidence of a high background prevalence of strongyloides infection in the Kimberley region (Hays 2015).

The diagnosis of strongyloides is complicated by the lack of a "gold standard". There is no data available on the impact of pregnancy on the predictive value of eosinophilia for strongyloidiasis – however pregnancy alone should not cause a rise in percentage eosinophils. There is no data available on the effect of pregnancy on strongyloides serology.

Parasites and anaemia

There is a paucity of high level evidence to guide recommendations regarding deworming in pregnancy. In a study of 3163 pregnant women in Uganda who were screened or both anaemia and helminthic parasites, neither hookworm infection nor strongyloides infection was associated with anaemia (Muhangi 2007). A smaller study in Papua New Guinea in an area of high parasite prevalence found the same (Phuanukoonnon 2013).

Another Ugandan study of 2507 examined the benefits of anti-helminthic treatment in pregnancy in an area where background infection with helminths was high (68% overall, 45% hookworm), deworming with albendazole or praziquantel during the second or third trimester was effective in treating parasitic infections, but had no overall effect on maternal anaemia, birth weight, perinatal mortality, or congenital abnormalities (Ndibazza J).

It is postulated that routine deworming in areas of very high hookworm prevalence may have benefits; however this is not applicable to the Kimberley region where hookworm rates are lower. Although data on the rate of hookworm infection in the Kimberley is lacking, in the Northern Territory hookworm was only detected in 134 out of 64 691 faecal samples (Davies 2013). Similar routine deworming practices in the Kimberley region make it likely that the prevalence of hookworm is similar to the NT.

Anti-helminthic medications in pregnancy

ADEC categorisation:
BENZIMIDAZOLES (Albendazole, Mebendazole)

> Avoid use in the first trimester (in animal studies albendazole is teratogenic in several species). In the second and third trimesters, single-dose treatment accounts for much of the experience in humans, although some prolonged courses have been documented in the first trimester; it has not been shown to be associated with congenital anomalies. Contact one of the pregnancy drug information centres for advice about a specific patient. Australian category D largely based on the concern about use in first trimester.

PRAZIQUANTEL: Appears safe; Australian category B1.
IVERMECTIN: Avoid use; Australian category B3.
PYRANTEL: Safe to use; Australian category B2.

Safety data from clinical trials:
The Entebbe study detected possible detrimental effect of albendazole treatment during pregnancy on the incidence of infantile eczema (Elliott 2011). Praziquantel was effective against Schistosoma spp. but poorly effective against hookworm. In other studies in non-pregnant populations, praziquantel had a greater response (Shaw 2010). The WHO has considered that congenital anomalies due to benzimadazoles are unlikely, and small observational studies have found no significant increase in congenital anomalies. The referenced RCT have shown no increase in perinatal mortality and infant survival to six months of age associated with the use of albendazole in second and third trimester. There is no evidence of genotoxicity or fetal toxicity with the use of praziquantel (Elliott 2011).

Efficacy data:
Pyrantel: In a study conducted by KPHU, 108 children were examined for parasitic infection by stool sample. Initial hookworm prevalence was 30.6%, strongyloides prevalence 1.9%. Pyrantel had no detectable effect against any parasites (Reynoldson). In RCTs, the egg reduction rate for hookworm

infection has ranged from 56.4 – 75%, however the number of patients included (152) is small (Keiser 2008).

Conclusion:
There is insufficient evidence of benefit to routinely offer deworming to pregnant women in the Kimberley region for the elimination of hookworm infection, whether or not they are anaemic. Pyrantel is safe to use in pregnancy but has been shown to have limited efficacy in the treatment of hookworm and strongyloidiasis.

Treatment for strongyloidiasis may be indicated on the basis of eosinophilia, positive serology and / or symptomatic infection and/or risk factors for complicated or disseminated infection – this should be discussed with an obstetric doctor first. If treatment is indicated, ivermectin is the most effective option (category B3), which should be given as two doses of 200mcg/kg PO, two weeks apart. If treatment is being considered, strongyloides serology should be performed prior to treatment to guide ongoing management.

Resources and references used:
Davies J., Majumdar SS., Forbes RTM., Smith P., Curries BJ., Baird RW, Hookworm in the Northern Territory: down but not out, MJA 2013; 198 (5): 278-281.

Elliott AM, Ndibazza J, Mpairwe H, Muhangi L, Webb EL, Kizito D, Mawa P, Tweyongyere R, Muwanga, M, Treatment with anthelminthics during pregnancy: what gains and what risks for the mother and child?, Parasitology, 2011:138 (12). pp. 1499-507. ISSN 0031-1820

Hays R, Esterman A, Giacomin P, Loukas A, McDermott R, Does Strongyloides stercoralis infection protect against type 2 diabetes in humans? Evidence from Australian Aboriginal adults 2015, Diabetes Research and Clinical Practice Volume 107, Issue 3, March 2015, Pages 355–361.

Keiser J, Utzinger J, Efficacy of Current Drugs Against Soil-Transmitted Helminth Infections: Systematic Review and Meta-analysis, JAMA 2008, 299: 1937-1948.

Larsson A, Palm M, Hansson LO, Axelsson O, References values for clinical chemistry test during normal pregnancy, Maternal medicine 2008, DOI: 10.1111/j.1471-0528.2008.01709.x www.blackwellpublishing.

Ndibazza J., Muhangi L., Akishule D., Kiggundu M., Ameke C., Oweka J., Kizindo R., Duong T., Kleinschmidt I., Muwanga M., Elliott AM., Associations between mild-to-moderate anaemia in pregnancy and helminth, malaria and HIV infection in Entebbe, Uganda, Clinical Infectious Diseases 2010;50:531-40.

MIlman N., Iron in Pregnancy – How Do We Secure an Appropriate Iron Status in the Mother and Child? Ann Nutr Metab 2011;59:50–54, DOI: 10.1159/000332129.

Muhangi L., Woodburn P., Omara M., Omoding N., Kizito D., Mpairwe H., Nabulime J., Ameke C., Morison LA., Elliott AM., Associations between mild to moderate anaemia in pregnancy and helminth, malaria and HIV infection in Entebbe, Uganda, Trans R Soc Trop Med Hyg (2007) 101 (9): 899-907.

Phuanukoonnon S., Michael A., Kirarock WS., Pomat WS., Van Den Biggelaar AHJ, Intestinal parasitic infections and anaemia among pregnant women in the highlands of Papua New Guinea, PNG Med J 2013 Sep-Dec;56(3-4):119-125.

Shaw JG1, Aggarwal N, Acosta LP, Jiz MA, Wu HW, Leenstra T, Coutinho HM, Olveda RM, Kurtis JD, McGarvey ST, Friedman JF, Reduction in hookworm infection after praziquantel treatment among children and young adults in Leyte, the Philippines, Am J Trop Med Hyg. 2010 Aug;83(2):416-21. doi: 10.4269/ajtmh.2010.09-0700.

Reynoldson JA1, Behnke JM, Pallant LJ, Macnish MG, Gilbert F, Giles S, Spargo RJ, Thompson RC, Failure of pyrantel in treatment of human hookworm infections (Ancylostoma duodenale) in the Kimberley region of north west Australia, Acta Trop. 1997 Dec;68(3):301-12.