POSITION STATEMENT

THE AUSTRALASIAN DIABETES IN PREGNANCY SOCIETY CONSENSUS GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH OF TYPE 1 AND TYPE 2 DIABETES IN RELATION TO PREGNANCY

September 2005

- **KEY RECOMMENDATIONS**

- Strict control of blood glucose levels should be pursued before conception and maintained throughout the pregnancy (Hb_{A1c} as close as possible to the normal range).
- High dose (5mg) folate supplementation should be commenced before conception.
- Oral hypoglycaemic agents should be ceased prior to conception.
- Diabetes complications screening should take place prior to conception.
- Management should be by a multidisciplinary team experienced in the management of diabetes in pregnancy.
- Blood glucose monitoring is mandatory during pregnancy.
- Targets are: Fasting 4.0-5.5 mmol/L; Post-prandial <8.0 mmol/L at 1 hour; <7mmol/L at 2 hours.
- A first trimester nuchal translucency (possibly with first trimester biochemical screening with PAPP-A and β-hCG) should be offered.
- Ultrasound should be performed for fetal morphology at 18 – 20 weeks, if required, for cardiac views at 24 weeks and for fetal growth at 28-30 and 34-36 weeks.
- Induction of labour or operative delivery should be based on obstetric and/or fetal indications.
- Level 3 neonatal nursing facilities may be required and should be anticipated when birth occurs before 36 weeks, or if there has been poor glycaemic control.
- Insulin requirements fall rapidly during labour and in the puerperium. Close monitoring and adjustment of insulin therapy is necessary at this time.

INTRODUCTION

The management of pregnancy in women who have Type 1 or Type 2 diabetes remains a challenging problem. The St Vincent declaration of 1989 set as a five-year target, the reduction of adverse pregnancy outcomes in women with Type 1 diabetes mellitus (T1DM), to a level equal to that of women without diabetes.[1] However, there is good evidence from many countries that this target has not been met.[2-7] There is often a lack of awareness of the dangers posed by diabetes for pregnancy, particularly with Type 2 diabetes (T2DM) which is increasingly common and often undiagnosed prior to pregnancy. Therefore in 2003, the Australasian Diabetes in Pregnancy Society (ADIPS) formed a working group comprising diabetes educators, endocrinologists, and obstetricians to formulate guidelines appropriate for the Australian setting. Where possible, literature searches were made through medline and further review of references in the papers examined. However, in may areas there was an absence of level 1 evidence and the combined experience and expertise of the writing group was drawn upon to arrive at the consensus guidelines. The core guidelines were published in the Medical Journal of Australia in 2005[8] (available at http://www.mja.com.au/public/issues/183_07_031005/mce10281_fm.html). The following is a more comprehensive document which provides further information which could not be included in the published guidelines.

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A. MANAGEMENT OF WOMEN WITH DIABETES PRIOR TO CONCEPTION

Information and counselling should be provided to all females of reproductive age with diabetes so that they are aware of the problems of diabetes in pregnancy, the potential dangers inherent in unplanned pregnancy and the benefits of prepregnancy counselling. The risks include increased perinatal mortality and malformation rates. These matters should be raised at each annual review of diabetic status or more frequently if required. A meta-analysis has demonstrated a significantly lower prevalence of major congenital anomalies in offspring women who attended for pre-pregnancy counselling (relative risk 0.36, 95% CI 0.22-0.59- absolute risk 2.1% vs 6.5%)[9].

General

General prepregnancy obstetric advice should be offered regarding the advantages of the following:

- a) cessation of smoking.
- b) reduced alcohol intake to within current NHMRC safety recommendations[10].
- c) review of all medications (including complementary) for safety in pregnancy.
- d) assessing immune status and screening for infectious diseases as recommended by the NHMRC.
- e) weight management and exercise prescription where appropriate.
- f) advice about contraception until conception is desired.

Diabetes Specific Measures

Management Personnel

A multidisciplinary team experienced in the management of diabetes in pregnancy has been shown, in many countries[11-14], to achieve superior obstetric and fetal outcomes relative to appropriate local comparators. This team should consist of people with an interest and experience in managing diabetes in pregnancy. Given the problems of health provider distribution and distances in Australia the personnel may have differing levels of expertise in different places. The team should consist of an obstetrician, endocrinologist (or physician experienced in diabetes care during pregnancy) diabetic educator and dietitian.[11-12] The importance of this preconception counselling and review cannot be underestimated.

Specific issues to be discussed by the management team include the clear benefits of optimal metabolic control prior to conception in reducing the risk of miscarriages, congenital malformations, perinatal mortality and other complications, and the benefits of taking folic acid 5mg daily for the prevention of neural tube defects[15] (see Note 1). Vitamin B12 levels should be measured in women taking metformin. The optimal glycaemic targets should be made clear. At present the minimum standard set by the National Diabetes in Pregnancy Advisory Council is to achieve and maintain a target HbA1c of <1% above the normal range (generally <7%).[16] However, there is evidence that the HbA1c should be maintained within the normal range if possible[5,7] (see Note 2), whilst avoiding hypoglycaemia, and this is to be encouraged. This should be achievable in most patients with T2DM, but may not be possible in women with T1DM. Women should not actively attempt pregnancy or embark on assisted reproductive treatment until the best available glycaemic control has been achieved. The review should include a reassessment of: diabetes education with the goal of ensuring adequate self-management skills including sick day care and hypoglycaemic management;

diet including suggestions for dealing with morning sickness; and, the physical activity regimen.

Medications

1. Insulin Analogues

There is increasing use of the newer rapid acting insulin analogues during pregnancy. There is more published information for lispro (Humalog®) than aspart (NovoRapid®) although a formal multicentre study will report shortly on the use of aspart in pregnancy. Recent cohort studies suggest that lispro is probably safe[17-19] despite early case reports to the contrary[20,21]. Two reviews have concluded that the published data do not suggest that lispro or aspart are teratogenic, nor are they associated with adverse effects in pregnancy.[22,23] Nevertheless, their use in pregnancy should be discussed with the woman. There is little published experience with glargine (Lantus®), the new long acting insulin analogue, with only anecdotal cases of safety reported[24,25]. A recent review draws attention to the increased mitogenic potential of this agent and urges caution in pregnancy[23].

2. Oral Hypoglycaemic Agents

The gold standard for pharmacological hypoglycaemic therapy in pregnancy is insulin. Oral hypoglycaemic agents are not currently recommended because there is limited information regarding their safety in pregnancy. A meta-analysis[26] suggests that the oral agents do not cause an increased risk of congenital malformations. Therefore they could be considered safe from this limited point of view. However, the authors themselves call for more data with oral agents in well controlled diabetes. ADIPS has recommended metformin therapy is not to be used routinely in women with pregnancies complicated by diabetes[27] and its use requires further investigation in formal clinical trials prior to possible adoption for more widespread

use in pregnancy. When the potential harm from metformin therapy is likely to be outweighed by its benefits however, metformin therapy could be considered. Such situations include refusal of the patient to use insulin[27]. When pregnancy occurs on oral agents they should not be stopped precipitously; rather an urgent referral is indicated for careful transfer to insulin therapy avoid hyperglycaemia in the critical early period of gestation.

3. Anti-Hypertensive Medication

Anti-hypertensive therapy in pregnancy has been reviewed by the Australasian Society for the Study of Hypertension in Pregnancy with guidelines formulated[28] There is considerable evidence supporting the use of methyldopa, oxprenolol, clonidine, labetolol, prazosin and nifedipine in pregnancy (see Note 3). ACE inhibitors should be avoided in pregnancy as they are hazardous for the fetus in the third trimester, and of unproven safety in the first.[29,30] If the woman has severe or difficult to control hypertension, it may be acceptable, after informed discussion, to continue the ACE inhibitor, ceasing it as soon as pregnancy occurs. The effect of angiotensin 2 receptor blockers in pregnancy is unknown, but it is expected that it would be similar to ACE inhibitors.

4. Lipid Lowering Medication

Fetal malformations have been documented in pregnancies where statins were continued in the first trimester.[31] They are contra-indicated in pregnancy.

Diabetes Complications Review

Formal assessment for diabetes complications is essential, particularly retinopathy and nephropathy. The medical practitioner should advise women with diabetic complications of the risks they may encounter during pregnancy. Because of the risk of progression, some of these complications represent contraindications to pregnancy.

Retinopathy: The eye examination should be conducted through dilated pupils by a person experienced in retinal examination. Pre-existing retinopathy may progress more rapidly in pregnancy.[32] Therefore, retinopathy which requires laser therapy should treated before pregnancy.

Nephropathy: Screen for nephropathy with an overnight or 24 hour urine sample to quantify the albumin excretion rate[33]. Failing this, an albumin/creatinine ratio on an early morning specimen is an alternative screening test. If the latter is >3.5mg albumin/mmol creatinine, a timed sample should be collected. Patients with pre-existing microalbuminuria are more likely to develop pre-eclampsia.[34,35] If renal function is significantly impaired (creatinine >0.2 mmol/L), there is an increased risk of progression to dialysis during pregnancy, and this should be considered a contraindication to pregnancy[36]. One third of such patients may die within 16 years[37]. The implications should be discussed with the woman planning pregnancy.

Macrovascular Disease: Evidence of macrovascular disease should be sought through detailed history and examination, and investigated if suspected. Pre-existing heart disease including coronary heart disease requires cardiological review prior to conception. Significant coronary artery stenosis should be treated prior to pregnancy.

Autonomic Neuropathy: The presence of autonomic neuropathy resulting in gastroparesis, orthostatic hypotension or hypoglycaemic unawareness may severely complicate the management of diabetes in pregnancy.

Complication	**Suggested Initial Screening Method**
Retinopathy	Fundoscopy through dilated pupils
Nephropathy	Timed urine sample or early morning urine sample
Macrovascular disease	History and examination

Autonomic Neuropathy	History and examination

Other Related Issues

Thyroid function should be measured for women with T1DM.[38,39] Abnormalities in women with T1DM are common and may adversely affect pregnancy outcomes (See Note 3). The possibility of other coexistent autoimmune disease (eg coeliac disease, pernicious anaemia) in women with T1DM should be considered (see Freemark et al for a discusion of pros and cons of screening for coeliac disease in children[40]).

B. MANAGEMENT DURING PREGNANCY

General Management

Women with diabetes should be managed by the specialised multidisciplinary team.It is recognised that in certain situations (eg isolated communities) some aspects of ideal pregnancy management may not be possible.

Medical

Routinely review the woman (possibly by telephone in some instances) every 1-4 weeks during the first 30 weeks and then every 1-2 weeks until delivery, depending on diabetes control and the presence of diabetic and obstetric complications. The assessment includes a review of glycaemic control. Self monitoring of blood glucose is mandatory. It is recommended that tests be performed fasting and 1-2 hours after meals. In addition, some testing before meals or overnight may be useful particularly in patients with T1DM. The blood glucose (BGL) targets are: fasting and preprandial 4.0-5.5 mmol/L. and post-prandial <8.0 mmol/L at 1 hour or <7mmol/L at 2 hours. A basal bolus regimen of insulin generally provides the best opportunity for good glycaemic control. Insulin pump therapy is a suitable alternative where there is local experience. The Hb_{Alc} should be monitored every 4-8 weeks and kept within the normal range. (Note that the Hb_{A1c} is normally lower in pregnancy but most laboratories do not report a normal reference range specific to pregnancy). Serious or sustained ketonuria should be avoided (see note 4). Note that the pregnant woman with T1DM is more prone than usual to ketoacidosis.

The woman should be monitored for signs or progression of diabetes complications particularly retinopathy and proteinuria. Formal eye review should be at least 3 monthly if baseline retinopathy is present, if there is a rapid improvement in glycaemic control, or if there has been a long duration of pre-existing diabetes.[41,42] Proteinuria should be assessed by dipstick at regular intervals, and quantitated where appropriate. The diabetes complications review should be repeated at the first antenatal visit if conception has been delayed.

Insulin Requirements: What to expect

Hypoglycaemia, especially overnight, is more frequent from the 6th to 18th weeks of gestation, and insulin doses may need to be decreased.[43] The physiological insulin resistance of pregnancy increases in the late second trimester, and may continue to increase after that time. Insulin requirements may increase substantially. Insulin requirements can fall after 32 weeks.[44,45] Any fall greater than 5-10% should lead to an assessment of fetal well-being and a search for medical conditions which can lead to loss of counter-regulatory control (eg adrenal insufficiency either primary or secondary). In the absence of abnormalities on fetal monitoring, a fall in insulin requirement does not correlate with adverse fetal outcome and is not in itself an indication for delivery.[44]

Tight glycaemic control needs to be balanced against the risk of hypoglycaemia. Maternal deaths due to hypoglyceamia have been reported.[46,47] It remains unclear if hypoglycaemia can adversely affect fetal development.[46] Modest maternal hypoglycaemia down to 2.5 mmol/L does not appear to affect fetal well-being.[48]

Unsatisfactory Glycaemic Control

If there is unsatisfactory metabolic control, potential sources of the problem such as diet, intercurrent illness, concurrent medication, stress, exercise and lifestyle need to be explored. Treatment needs to be reviewed and adjusted. It may be necessary occasionally, to admit the woman to hospital to optimise glycaemic control. If not already under the care of a team specialising in the care of diabetes in pregnancy, then the woman should be referred.

Obstetric Management

Regular routine obstetric review is based on a high-risk pregnancy. Normal fetal growth and indices for fetal and maternal welfare should be maintained. Midtrimester maternal serum screening for aneuploidy is less reliable in the presence of diabetes. Consideration should be given to the use of first trimester screening using nuchal translucency at 12-13 weeks, with β-hCG and PAPP-A measured at 10-13 weeks where resources are available.[49] Because of the need for accurate dating, a first trimester ultrasound examination should be performed even when aneuploidy screening is not desired.

Ultrasound examination for fetal morphology should be offered at 18-20 weeks. In selected cases, repeat morphology scanning at 24 weeks may help to better define cardiac structures. Further examinations to assess fetal growth should be performed at 28-30 weeks and repeated at 34-36 weeks. The latter will help to determine the timing and route of delivery. Further ultrasound examination, including umbilical artery Doppler flow measurements, may be indicated in the presence of other abnormalities. Formal testing of fetal well-being (e.g. cardiotocography, umbilical Doppler blood flow studies or biophysical profile) is not necessary in an otherwise uncomplicated pregnancy before 36 weeks gestation.

Medications Used in Management of Premature Labour

Some pharmacological agents, administered when a premature delivery is likely, may lead to significant hyperglycaemia and risk of ketoacidosis in women with diabetes.[50-52] These include betasympathomimetic agents (eg salbutamol) given to suppress uterine contractions (tocolytics) and corticosteroids given to enhance fetal lung maturity. Following administration of salbutamol there may be a rapid rise in BGL.[50-52] Therefore, alternative tocolytic agents such as nifedipine are recommended. Following administration of corticosteroid, the rise in BGL usually starts about 6-12 hours later, and may persist for up to 5 days[51,52] It is important in this setting to maintain good glycaemic control to reduce any further metabolic stress on the fetus with BGL monitored every 1-2 hours until glycaemic control has stabilized and insulin requirement returned to baseline. When hyperglycaemia occurs, consideration should be given to the commencement of an intravenous insulin infusion. This should be titrated to keep the BGLs in the target range. Insulin requirement varies markedly with rates being anywhere from 2-30 units insulin per hour.[50,52] There should be a local protocol to proactively manage the anticipated hyperglycaemia[50,51].

Type 2 Diabetes in Pregnancy

A recent survey of 10 teaching hospitals by ADIPS has found that in pregnancies complicated by pre-existing diabetes, T2DM is at least as common as T1DM.[2] T2DM in women of reproductive age is particularly common amongst Aboriginal and Torres Straight Islander peoples, and other ethnic groups such as people from Pacific Islands, Asia (particularly from the Indian subcontinent) and the Middle East. With the increasing prevalence of T2DM amongst women of reproductive age, there are some specific issues which need to be considered.

The treatment targets and complications screening are as for T1DM. Some women with diet controlled T2DM may require no pharmacologic hypoglycaemic treatment during early pregnancy. Insulin is usually required later in pregnancy. Oral hypoglycaemic agents are not recommended in pregnancy. Exceptions to this practice should only be made after review by the specialised management team. Women with pre-existing impaired glucose tolerance or impaired fasting glycaemia should be managed as if they had gestational diabetes from the time of confirmation of pregnancy.

The risk of congenital anomalies amongst women with T2DM is similar to those with T1DM. A recent New Zealand study found a congenital malformation rate of 6.6 times the background rate for women with T1DM and 4.9 times for T2DM.[53] The same NZ group identified a 3.7 times higher perinatal mortality rate for T2DM than for T1DM (46.1/1000 vs 12.5/1000).[54] The ADIPS survey of 10 teaching hospitals in Australia found very similar increased rates for both major congenital malformations and stillbirth in T2DM compared to the general population.[2] T2DM should therefore not be considered a more "benign" form of diabetes than T1DM in pregnancy. It is often also accompanied by obesity and other features of the metabolic syndrome which carry their own increased perinatal risk[55,56].

C. MANAGEMENT DURING DELIVERY

Document in advance, a plan for insulin management during delivery and in the immediate postpartum that is communicated to all parties, including the patient.

Delivery

Woman with pre-existing diabetes should be delivered at term unless obstetric or medical factors dictate otherwise (e.g. fetal macrosomia, polyhydramnios, poor metabolic control, pre-eclampsia, IUGR). Vaginal delivery is preferable unless there is an obstetric or medical contra-indication. Where the estimated birth-weight exceeds 4,250–4,500g, the risk of shoulder dystocia warrants consideration of elective caesarean section.[57] The need for induction of labour and/or assisted delivery should be based on obstetric and/or fetal indications. The need for access to specialized neonatal intensive care should be based on fetal risk. The need for level 3 neonatal nursing facilities should be anticipated when birth occurs before 36 weeks, or if there has been poor metabolic control.

Protocol for Diabetes Management During Labour

The woman should continue her regular diet, insulin and blood glucose monitoring until in labour. When in active labour the blood glucose should be measured every 1-2 hours. The blood glucose should be kept within the range of 4-7 mmol/L. Guidelines for management of diabetes in labour vary widely. There is no evidence to prove one method superior to others. A locally accepted protocol should be in place. Options include:

i) routine insulin infusion (usually with co-administered dextrose)

ii) insulin/dextrose infusion only if BGL<4 or >7 mmol/L

iii) subcutaneous insulin injections

iv) continuation of continuous subcutaneous insulin infusion (insulin pump therapy)

Some women may be managed safely with good glycaemic control without the need for insulin therapy in labour.

Protocol for the Management of Diabetes during Caesarean Section

Elective caesarean section should be scheduled first on the morning list, and the usual dose of intermediate insulin given the night prior. Long acting insulins may require a dose reduction to avoid hypoglycaemia in the post partum period. Women with T1DM may require an insulin/dextrose infusion because of the prolonged fasting. An emergency caesarean section will require a flexible approach to ensure glycaemic stability and prevent hypoglycaemia immediately postpartum.

D. POSTPARTUM MANAGEMENT

Pregnancy often leads to a rejuvenated interest in ideal care of diabetes, and sometimes initiates the first contact with a diabetes team for some time. It is important to organise an appointment for diabetes review within 1-2 months of delivery, and ensure that ongoing diabetes care occurs. A management plan should be developed prior to discharge including specific contact details (general practitioner, endocrinologist, diabetes educator, local Diabetes Centre) in case any problems with glycaemic control occur following discharge. Hypoglycaemia is a particular issue in this unpredictable period.

Type 1 Diabetes

Insulin requirements begin to decrease during labour and fall rapidly after delivery. Close monitoring and re-stabilisation will be necessary in the first few weeks post-partum. The primary treatment goal in the unpredictable post-partum period is to avoid hypoglycaemia. It is important to discuss measures to avoid hypoglycaemia such as ensuring midmeals and meals that are due are not delayed, and setting up a specific infant feeding area in the home with snacks readily available. Appropriate management of hypoglycaemia should also be revised at this time. Specific advice should be given about nocturnal hypoglycaemia. The new mother should be reassured that a short-term relaxation of tight control is justified to reduce te risk of hypoglycaemia.

A significant fall in blood glucose may occur during breastfeeding, and therefore the risk of hypoglycaemia is accentuated. Breastfeeding women should be encouraged to test their blood glucose levels before and after breast feeds initially, to ascertain if specific precautionary measures (such as maintaining higher blood glucose levels) need to be undertaken.

Type 2 Diabetes

For many women, diet alone will achieve good glycaemic control after delivery and insulin may be ceased. Blood glucose levels should be monitored to determine whether medication needs to be recommenced. If treatment is required, insulin is recommended if breast-feeding. The WHO[58] states that oral hypoglycaemic agents are not contraindicated although metformin does pass to the child.[59] They recommend monitoring the baby for hypoglycaemia. However, several members of this panel believe that this exposure is unwarranted in most situations. Some women may require ongoing insulin therapy for maintenance of good glycaemic control.

Contraception

It is important to discuss contraception before discharge from hospital. There is no evidence that any of the present contraceptive methods is contraindicated in women with diabetes. All available options should be discussed with the woman and her partner.

E. NEONATAL MANAGEMENT

This area was not addressed by the panel. One source of information regarding this is the Neonatal Handbook[60]. A comprehensive review of the management of neonatal hypoglyceamia has been conducted by the WHO[61].

F. IMPLICATIONS FOR THE OFFSPRING

Diabetes during pregnancy has far reaching implications for the child in infancy and in later life. There is good evidence that an adverse intrauterine environment, independent of any genetic determinant, is a factor in later metabolic disturbances in the offspring of the diabetic mother. Studies have shown that obesity, impaired glucose tolerance and T2DM are more prevalent in children and adults, when diabetes was present during their fetal development.[62-64] This is assumed to be due to maternal hyperglycaemia during pregnancy and emphasises the importance of good glycaemic control during pregnancy. Attention to long-term healthy lifestyle practices for the whole family may minimise the risk of diabetes in other family members.

NOTES

Note 1. Folic Acid Supplementation

Five milligrams folic acid supplementation is recommended. A review of studies of folic acid suppplementation in pregnancy predicted that 5mg folate daily would reduce the risk of neural tube defects by 85%, an effect substantially greater than with 0.4 mg or 1 mg daily.[15]

Note 2. Hb_{A1c} Target

There is a widely held belief from the older literature, that there is a threshold glycosylated haemoglobin below which the risk of congenital malformations is not increased. In a review of this literature in 1996, Kitzmiller et al concluded that an initial pregnancy HbA1c <5 standard deviations (SDs) above the mean (equivalent to a HbA1c <7.5% where the normal range is 4.0-6.0%) is sufficient to prevent an excess rate of major congenital malformations.[13]

More recent studies challenge this belief in both Type 1 and Type 2 diabetes. Towner has found amongst women with T2DM who had an initial pregnancy HbA1c within the normal (non-pregnant) range, the malformation rate was double that of the background population.[4] There was a further doubling in malformation rate to 11% amongst pregnancies where the HbA1c was 2-4 SDs above the mean. This equated to an HbA1c up to 1.3% above the normal range. In a study of subjects with T1DM, Suhonen found that even an HbA1c slightly above the normal range (2-4 SDs above the mean, equivalent to an HbA1c up to 1.2% above the normal range) had a malformation rate triple that of control pregnancies.[5] In a recent English study the congenital malformation rate in women with a glycosylated haemoglobin of < 7.5% (mean + 5 SDs) was still 2.4 times that of the background population.[6] The adverse effects of hyperglycaemia on pregnancy are further highlighted by Mills et al who reported that an

increase of one standard deviation (equivalent to 0.5% where the normal range is 4.0-6.0%) in a first trimester glycosylated haemoglobin increased the risk of spontaneous abortion by 3%.[65]

We interpret these data to indicate that we should ideally target a pre-pregnancy glycosylated haemoglobin within the normal range. Not all women with diabetes can achieve this. The decision to accept less than ideal control should be made on an individual basis by a physician experienced in diabetes management following a discussion with the woman concerned

Note 3 Thyroid Function

In pregnancy TFTs should be assessed against a normal range derived for the appropriate gestation of pregnancy. TSH is depressed in the first half of pregnancy and free T4 and free T3 are often slightly high. Later in pregnancy free T4 may fall below the normal non pregnant normal range and TSH may remain low.[66]

Note 4. Ketonuria

The adverse effects of ketonaemia on the fetus are still a matter of debate. This may in part reflect the difficulties in assessing ketonaemia from urinalysis.

The pregnant woman is particularly prone to ketosis and ketones readily cross the placenta. Although ketones are used by the fetus as a source of energy, an early study suggested that maternal ketosis is harmful to the fetus, particularly in neuropsychological development.[67] However, doubts regarding these findings have been raised by others[68], as the study did not take uncontrolled diabetes and other factors into consideration. A subsequent study of calorie

restriction in pregnancy for obese women with diabetes did not demonstrate any harmful effects of mild ketonuria.[69]

We conclude that it would be prudent to avoid ketosis in pregnancy when this can be readily achieved although there is no evidence to suggest that occasional mild ketonuria has any deleterious effect on fetal growth or development.

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